MEASURING THE POTENTIAL UNINTENDED CONSEQUENCES OF NATIONAL POLICY AIMED AT REDUCING ANTIBIOTIC PRESCRIBING IN PRIMARY CARE IN ENGLAND

Sabine Bou-Antoun

Imperial College London, Department of Primary Care and Public Health

PhD in Clinical Medicine Research (Public Health)

2020

Thesis submitted for the degree of Doctor of Philosophy of Imperial College London

DECLARATION OF ORIGINALITY

I, Sabine Bou-Antoun, confirm that the work presented in this thesis is my own, and if otherwise, has been appropriately acknowledged and referenced where relevant.

COPYRIGHT DECLARATION

ETHIC APPROVAL

Elements of the research reported in this thesis used primary care, secondary care and mortality data containing patient-level information. Use of these data required approval from the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research. ISAC approval was obtained for this research on the 30 November 2016, (protocol number: 16_129R; Appendix 16 and Appendix 17).

ACKNOWLEDGEMENTS

My thanks to the National Institute for Health Research (NIHR) for funding this PhD. My very sincere thanks to my supervisors Professor Paul Aylin (Imperial College London [ICL]), Professor Alan Johnson (Public Health England) and Dr Ceire Costelloe (ICL) for their support, insight and guidance. Thank you to Professor Alison Holmes (ICL), Dr Kate Honeyford (ICL), Dr Myriam Gharbi-Drysdale, all my colleagues and fellow PhD students at the Health Protection Research Unit. It has been a privilege to work amongst such personable and inspiring researchers, thank you for the 'fellowship' and laughs. Thanks go to Ms Mahsa Mazidi (ICL) for the data management support, and along with room 319 colleagues, for being kind friends and great company during late nights. Thanks to Dr Violeta Balinskaite (ICL) for being the second reviewer for the systematic review, and to Dr Benedict Hayhoe (ICL) for his clinical advice on CPRD Read code selection. Alongside Dr Hayhoe, thanks also go to four experts who were involved with defining respiratory infection pathways: Dr Alex Chen (ICL), Dr Kay Wang (University of Oxford), Prof Gail Hayward (University of Oxford), Prof Nicholas Francis (Cardiff University). Thanks go to Ms Fran Husson and Mr Tim Sims, for kindly providing a patient's perspective on the research.

I'd like to thank teachers along my educational path; Mr Aldridge for teaching me how to construct my first English sentence, Mrs Turner for giving me the love of science, and Mrs Wood for being an amazing mentor.

Finally, my immeasurable thanks to my family and friends, particularly my sister and mother-in-law, for their endless support, kindness and humour. To the child genius that is my niece and my little wild nephew, you have been the best distractions. To my incredible parents for always pushing me to do more and being my constant source of inspiration. To my husband, for sharing the highs and lows, helping me keep things in perspective and for your faith in me, thank you. Lastly to my little girl, my most precious of achievements during my PhD years and the most incredible being in my life.

ABSTRACT

Background

Inappropriate antibiotic use is a known driver of antimicrobial resistance. Primary care antibiotic prescribing accounts for approximately 80% of antibiotic consumption in England, with respiratory tract infections (RTIs) being the most common indication. RTIs are largely viral and self-limiting, and antibiotics are often inappropriate. The 2015/16 NHS England Quality Premium (QP) financially incentivised reductions in primary care antibiotic prescribing. This may have led to unintended consequences such as a reduction in appropriate antibiotic treatment with some patients developing more severe infections.

Aim

To assess the reduction in antibiotic prescribing following introduction of the 2015/16 QP, and the occurrence of unintended consequences in patients presenting to English general practices with RTIs, as measured by re-consultations, severe infections (in primary and secondary care) and death.

Methods

A systematic literature review and meta-analysis were undertaken pooling evidence on the risk of RTI complications where there was lack of exposure to timely antibiotic treatment. This contributed to a modified Delphi method, defining RTI infection pathways. Subsequent investigations of the potential impact of the QP used linkage of routinely collected national healthcare datasets. Interrupted time series analysis (ITSA) and hierarchical multivariable analysis were the statistical methods utilised, comparing antibiotic prescribing for RTIs in general practices across England, and unintended consequence (measured by re-consultations, severe infections and death, within 30-days of an initial RTI) pre- and post-QP.

Results

The systematic review found that RTI complications were rare. The pooled odds ratio favoured the use of antibiotics in preventing RTI complications. There was a high-level of heterogeneity between studies, high risk of bias (particularly indication bias) and studies were often not powered or designed to assess complications. ITSA demonstrated that antibiotic prescribing for RTIs decreased over the six-year study period, with a significantly decrease coinciding with the introduction of the QP (decline was particularly evident in children, <16y). The ITSA assessing potential impact on unintended consequences did not find evidence of greater risk of re-consultation, or in complications reported in general practices, hospital admissions, or mortality. However, increases in complications (e.g. pneumonia in primary care and bloodstream infections in secondary care [p>0.05]) were reported, particularly for elderly patients (≥65 years) and patients who had been prescribed antibiotics; increased mortality was also noted, although this was not sustained. Complications were shown to have been on a gradual rise prior to the QP, hence findings from the multivariable analysis may reflect this increase. Findings from this analysis also showed a significant reduction in antibiotic prescribing post-QP, and greater odds of complications in patients who had been prescribed antibiotics compared to those who had not.

Conclusions

The 2015/16 QP has been safely implemented with no significant unintended consequences. Future reductions in antibiotic prescribing should be tailored based on infection indication and patient risk factors (e.g. by age/elderly). Future surveillance would benefit from improvements in national primary care data acquisition, linkage and surveillance of unintended consequences.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS

AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AOM	Acute otitis media
APRHAI	The advisory committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infections
ARHAI	The advisory committee on Antimicrobial Resistance and Healthcare Associated Infection (later named APRHAI)
ASG	Antimicrobial stewardship subgroup
BNF	British National Formulary
BSA	Business Services Authority
BSA	The NHS Business Services Authority
CASP	The Critical Appraisal Skills Programme checklist
CCG	Clinical Commissioning Groups
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CMO	Chief Medical Officer
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CQUIN	Commissioning for Quality and Innovation
CSU	Commissioning Support Unit
DDD	Defined Daily Dose
ESPAUR	English Surveillance Programme for Antimicrobial Utilisation and Resistance
GP	General practitioner
HCAI	Healthcare-associated infection
HES	Hospital Episodes Statistics
HIC	High-income countries
HPRU	Health Protection Research Unit
IPC	Infection prevention and control
ISAC	Independent Scientific Advisory Committee
ITS	Interrupted time series

ITSA	Interrupted time series analysis
JPIAMR	Joint Programming Initiative in AMR
LMIC	Low- and middle-income countries
MDR	Multidrug resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics
OR	Odds Ratio
PHE	Public Health England
QOF	The Quality and Outcomes Framework
QP	Quality Premium
RCT	Randomised controlled trial
RTI	Respiratory tract infection
SMAC	Standing Medical Advisory Committee
SSTI	Skin and soft tissue infection
STAG-AMR	The WHO convened Strategic and Technical Advisory Group on AMR
STAR-PU	Specific Therapeutic group Age-sex Related Prescribing Units
TARGET	"Treat Antibiotics Responsibly, Guidance, Education Tools" toolkit
UK	United Kingdom
USA	United States of America
UTI	Urinary tract infection
WHA	World Health Assembly
WHO	World Health Organisation

CHAPTER 1

1 INTRODUCTION

1.1 Antibiotic discovery and resistance, the history

In 1928, Sir Alexander Fleming made the fortuitous observation that a mould which had contaminated an agar plate in which he had been culturing the bacterium *Staphylococcus* aureus, appeared to inhibit the growth of and destroy bacterial colonies. Fleming correctly speculated that the mould (*Penicillium notatum*) produced a diffusible substance capable of killing bacteria. This antibacterial substance, which was given the name "penicillin" was the first reported antibiotic.[1] The purification and chemical characterization of penicillin in the early 1940s,[2] and its subsequent use in humans paved the way for the successive discovery of other efficacious antibiotics and revolutionised medicine and the management of serious bacterial infections. Along with improvements in social determinants of health (e.g. diet, housing, sanitation), subsequent decades saw reductions in morbidity and mortality, particularly those associated with common infections such as pneumonia, acute rheumatic fever, meningitis and sepsis.[3, 4] The use of antibiotics has been correlated with an increase in the life expectancy of patients with inherited disorders and those with chronic conditions such as cystic fibrosis,[5] and has also benefited and permitted advances in many other treatments that would otherwise impose a high risk of life-threatening infections, i.e. treatments that would normally require or result in immunosuppression, such as surgery, organ transplantations, diabetes management, or chemotherapy for cancer.[4-7]

The discovery of antibiotics marked the beginning of what is known as the antibiotic era, which had seen the development of a number of new classes of antibiotics (Figure 1-1). However, this growing availability of antibiotics and the inexorable increase in prescribing, often involving both overuse and inappropriate use (i.e. that is the use of antibiotics for inappropriate indications, dose or duration and the unnecessary use of broad-spectrum antibiotics [antibiotics active against a wide range of bacterial species, often both Gram-positive and Gram-negative bacterial groups] for the treatment of common

uncomplicated infections) has resulted in the bacteria of which these antibiotics are used against, relentlessly developing tolerance, or what is commonly described as resistance. In addition to antibiotics, which are drugs that are active against bacteria, other agents have been developed that are active against viruses (anti-virals) fungi (anti-fungals) and parasites (anti-parasitic agents), with all of these agents grouped under the generic term "antimicrobials". The World Health Organisation (WHO) defines antimicrobial resistance (AMR) as "resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it".[8]

As seen in Figure 1-1, there is a temporal relationship between the use of antibiotics and subsequent emergence of bacteria resistant to these drugs. Resistance to antibiotics was indeed noted as early as 1942, subsequent to the use of the first antibiotics in the 1936.[9] In his Nobel Prize lecture in 1945, Fleming himself pointed out that the inappropriate use of antibiotics poses a risk of resistance:

"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."[10]

The use of antibiotics in this way demonstrates Darwin's concept of "Survival of the Fittest", in that when bacterial populations are exposed to antibiotics either *in vitro* or *in vivo*, susceptible bacteria are eliminated but any resistant variants persist.[11] Over time, through continued exertion of selective pressure, bacterial strains with inherent resistance, or those that have acquired or developed resistance to antibiotics in order to "survive" instead accumulate and replace the original susceptible populations, resulting in antibiotics which were previously clinically effective losing their potency.[12] Thus, antibiotics and other antimicrobials are vastly different from other medicines, in that their overuse results in them becoming clinically less effective, and the efficacy of antibiotics in a patient is

affected not only by the use of antibiotics by that patient, but also by the use in other patients and the wider population.[13]

The problem of AMR is one of global dimensions, as resistant bacteria know no borders. As a result of increasing international travel and globalisation, resistant strains, particularly those that are resistant to multiple antibiotics (referred to as multidrug resistant [MDR]), may spread between countries and continents, creating an increasingly global threat to public health.[14] An Antimicrobial Resistance Review has reported that approximately 700,000 deaths per year occur globally due to infections caused by resistant microorganisms, with an estimation of this reaching 10 million per year by 2050 if appropriate actions are not taken.[5] This will without doubt also have an economic impact, with AMR infections frequently resulting in worse clinical outcomes, longer hospital stays and longer illness durations, higher medical costs and increased morbidity and mortality.[6, 15-17] The review reported that AMR infections could cost 100 trillion USD in terms of lost global production by 2050 if no action is taken.[5]

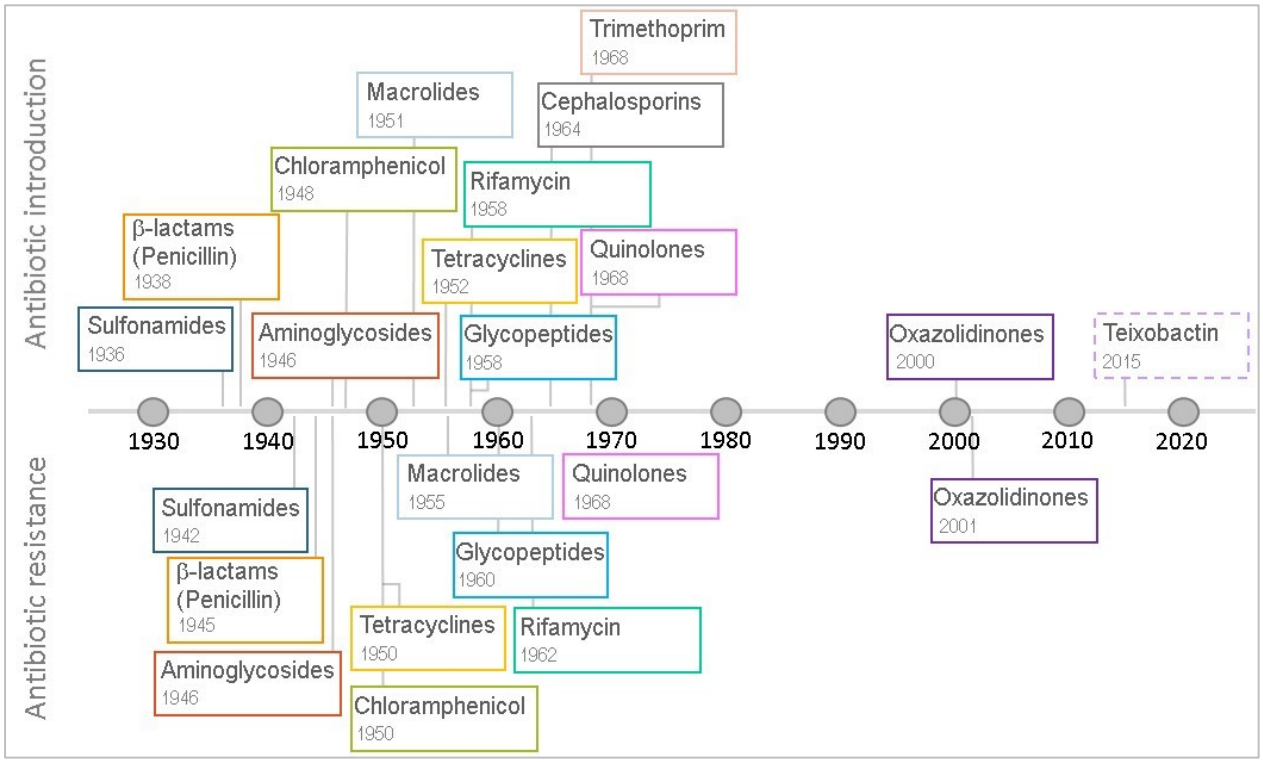
An additional challenge to estimating the burden of AMR is that much research to date has focused on AMR driven by human behaviour, with uncertainty around the additional impact of animal-human-environmental interactions and the antibiotic use and resistance in these fields.[18] This is important as more than half the antibiotics produced annually are given to animals (both domestic and wildlife) rather than humans.[19] As a result, animals may harbour antibiotic-resistant bacteria, which not only poses a threat to animal health, but also provides a reservoir of resistant bacteria that may pass directly or indirectly (e.g. through the food chain) to humans.[12, 19, 20]

A particular concern with the spread of AMR is that increases in the burden of bacterial resistance have not been matched with fast paced antibiotic innovation, but rather been accompanied by declining investment in and discovery of new antibiotics, with pharmaceutical companies withdrawing funding for research and development of new antibacterial drugs.[13, 18] This is reflected by the fact that

following a peak in the 1950s, the discovery and introduction of new antibiotic classes dates back to the previous century (Figure 1-1), with nearly all the antibiotics licensed for use over the past 30 years being derivatives of known antibiotic classes.[18] The declining interest from the pharmaceutical industry is thought to be due not only to the scientific difficulty in discovering new antibiotics, but to the complexity and huge cost of undertaking clinical trials as part of the licensing process, and the fact that antibiotics are commercially unattractive (in that patients take antibiotics for a brief amount of time and clinicians are discouraged from prescribing them), unlike long-term treatments for chronic diseases such as diabetes.[18]

In the absence of new antibiotics that could be used to treat infections caused by bacteria resistant to currently available agents, other mitigation strategies are used to try to slow the spread of AMR. Theses predominantly comprise actions to prevent infections as this reduces the need for antimicrobial therapy, and include improvements in the uptake of vaccines, improved hand hygiene, and urinary catheter care, seeking alternative therapies to treat infections, and developing and providing point-of-care diagnostic tests (such as C-reactive protein tests) aimed at better and more rapid diagnosis of infection.[18, 21]

Figure 1-1: Timeline of the introduction after discovery of antibiotics and the emergence of resistance to them



Hand drawn, adapted from Lewis 2013,Clatworthy 2007, and Ling et al 2015.[9, 22, 23]
Note: Dotted box (Teixobactin) depicts discovered drug, however yet to be produced.
Note 2: The emergence of antibiotic resistance does not necessarily imply that the antibiotic class is clinically ineffective or that it is no longer used.

1.1.1 Drivers of antimicrobial resistance

The mechanisms by which bacteria develop resistance are biological, however the drivers of AMR are heavily influenced by human behaviour. Although antibiotic resistance seems inevitable, until the pharmaceutical industry re-engages with antibiotic production and until a new antibiotic emerges, the temporary solution (albeit an on-going solution also required to maintain the efficacy of any future antibiotics) would be to slow the rate of resistance by targeting social influences of the drivers of AMR. These include national and international travel (by which people harbouring antibiotic-resistant bacteria disseminate them within and between countries), consumption of antibiotics in veterinary medicine and food production, the culture of over prescribing, the perception of risk, suboptimal prescribing or lack of assured quality antibiotics, and suboptimal rapid diagnostics required for rational therapeutics, to name a few.[11, 12, 24] The link between the global ecology of antibiotic consumption and

subsequent resistance has had increasing attention and is thought to be the main determinant of resistance.[24] In high income countries, although the epidemiology of AMR is complex, it has been well documented that the over and misuse of antibiotics is a known driver for the emergence and spread of resistant bacterial strains.[25] Low and middle income countries are presented with a different challenge in that there is difficulty with access to healthcare, to firstly reduce the prevalence and severity of infections and secondly in attaining medicines where required. In these settings there is a need to preserve and improve access to antibiotics, whilst avoiding inappropriate and excessive use.[11]

The notion that antibiotic consumption is a known driver of AMR has been supported by evidence which demonstrates that higher antibiotic resistance rates seen in European countries are for those same countries with higher antibiotic prescription rates, although such a correlation does not prove a causal relationship.[26] Arguably, more convincingly, two systematic reviews researching the association of community antibiotic prescribing and resistance observed that prior antibiotic exposure at individual patient level was linked to subsequent carriage of resistant bacteria for up to a year, with further findings showing a correlation between areas with higher antibiotic consumption and higher resistance rates in certain pathogens.[6, 27] As antibiotic consumption has increased so has the erosion of antibiotic efficacy, with physicians increasingly forced to use antibiotics that were previously thought of as “last resort”, notably carbapenems; with consumption of carbapenems increasing in England prior to 2014 (antibiotic consumption peaked in 2014).[15, 28] As a result resistance to carbapenems is now proliferating. Carbapenem use and AMR has traditionally been centred among hospitalised patients, however resistant pathogens are now increasingly being isolated in the community setting.[15]

Antimicrobials are amongst the most commonly prescribed drugs in humans, however it is believed that up to 50% of these prescriptions are unnecessary,[12] with between 20-80% of antibiotics prescribed in primary care for common infections reported to be inappropriate, as many common infections, particularly those involving the respiratory tract, are of viral aetiology.[3] Efforts to reduce this over and

inappropriate use of antibiotics focus on promoting timely and correct use of antibiotics, at the most appropriate dose, route and duration, for the right infection, in so doing optimising clinical outcomes whilst minimising unintended consequences including resistance and toxicity.[25]

1.2 Antibiotic prescribing trends

Between 2000 and 2015, antibiotic consumption continued to rise globally, with a reported increase measured at a staggering 65% (21.1-34.8 billion defined daily doses [DDDs]).[29] The increase was primarily driven by low- and middle-income countries (LMIC), although high-income countries (HICs) also exhibited a modest increase and remain the highest prescribing countries.[29] The rise in consumption has been linked to growth in antibiotic use in Brazil, Russia, India, China and South Africa (known as the BRICS).[11] As LMICs have a higher disease burden, greater consumption in these countries could be reflective of necessary antibiotic use, although robust antibiotic consumption and AMR surveillance in these countries is often lacking.[29-31] Of notable concern is the global growth in the use of last resort antibiotics, such as carbapenems.[29]

There are wide variations in community antibiotic prescribing rates, both within the UK and when comparing the UK with other European countries.[26, 32] Community (i.e. outside of hospitals) consumption of antibiotics in the UK (2016: 19.6 DDDs per 1000 inhabitants per day) was lower than the European average of 21.9 DDDs per 1000 inhabitants per day, however this was still much greater than prescription rates seen in other European countries (e.g. the Netherlands 10.4, Sweden 12.0 and Germany 14.1 DDDs per 1000 inhabitants per day).[32, 33] Internationally and within countries, there are variations in the social determinants of health (e.g. socio-economic, cultural and environmental conditions),[34] data collection methods/surveillance, incidence and epidemiology of infections, the case-mix of patients and the underlying populations, which adds difficulty in generalising and comparing antibiotic prescription rates from one country to another. There is however an assumption that there should not be such a vast difference in prescribing between high-income countries in Europe

as there is little evidence that variations are associated with significant differences in recovery rates, infection severity or comorbidities.[13, 35]

1.2.1 Primary care antibiotic prescribing and infections

The majority of antibiotics used in humans are prescribed in primary care.[36] In Europe, primary care antibiotics prescriptions account for approximately 80-90% of total antibiotic prescribing.[26, 36] The England proportion corroborates this, with 78.5% of prescribing reported in general practices.[37] Furthermore, increases were seen in prescribing of antibiotics in the community setting early on in the second decade of this century, with the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report showing a 6% increase in the total use of antibiotics from 2010 to 2013, with a 4% increase in use seen in the general practice setting.[37] There is vast variation in antibiotic prescribing between regions and general practices within the UK, that is not entirely explained by differences in patient case-mix, local indices of deprivation or patient characteristics, such as age, clinical presentation, or comorbidities.[25, 38] Such observed variation in antibiotic prescribing is potentially indicative of inappropriate and over use of these drugs.[39] Recent conservative assumptions suggest that between 8.8% and 23.1% of antibiotic prescriptions in England are inappropriate.[40]

The reasons why a large proportion of antibiotic prescribing, with prevalent over- and inappropriate prescribing, is seen in general practices is multifactorial. The following factors have been reported to contribute to the innumerable pressures which may incline a general practitioner (GP) to prescribe antibiotics:

- beliefs around patient expectations of an antibiotic prescription,
- insistent patients requesting antibiotics,
- prognostic uncertainty with difficulty in differentiating between bacterial and viral infections leading to empirical prescriptions,

- limited time and facility for microbiological investigations with lack of point-of-care rapid diagnostic tools,
- beliefs that antibiotics may aid in alleviating symptoms and prevent complications where infection is bacterial,
- the threat of litigation where bacterial infection is missed,
- and the notion that prescribing may reduce repeat consultations.[3, 41-45]

Inappropriate antibiotic prescribing predominantly occurs for common conditions consulted for in primary care that are often self-limiting (i.e. conditions which resolve without necessitating the use of antibiotics).[46, 47] Respiratory tract infections (RTIs), urinary tract infections (UTIs) and skin and soft tissue infections (SSTIs) are the most common reasons for patients to consult with their GPs and concurrently the most common indications for empirical antibiotic prescribing in primary care.[46, 47] RTIs are the leading indication for antibiotic prescribing in primary care, with 46% of prescriptions linked to conditions of the respiratory tract.[26] Hutchinson *et al.* showed that high-prescribing physicians, compared to low-prescribers, diagnosed significantly more bacterial infections, and that the rate of diagnoses of UTIs and SSTIs were similar between high- and low-prescribers, with the rates driving the variations due to differences in the rate of diagnosis of RTIs.[48] Supporting published research has also shown that variation in prescribing between general practices in England were predominantly driven by differences in prescribing for RTIs.[40, 49, 50]

The most common acute RTIs include the common cold, acute sore throat and cough, pharyngitis and tonsillitis, acute otitis media (AOM), rhinosinusitis (rhinitis, acute sinusitis), laryngitis and acute bronchitis.[36] As mentioned above, inappropriate antibiotic prescribing is prevalent in primary care, and is particularly evident with RTIs, with approximately 36% of common colds, 40% of sore throats, 70% of AOM and 90% of sinusitis being prescribed antibiotics, despite national UK guidance recommending no antibiotic or a delayed antibiotic strategy for these indications.[51] These RTIs rarely lead to complications and antibiotics often offer minimal benefit as the infections are predominantly viral in

aetiology and often self-limiting.[52] The use of antibiotics for common infections are of continual debate for these reasons. Furthermore, there has not been any clear understanding of the underlying reasons for the increases in prescribing, or differentiation between whether there has been an increase in the incidence of infections and therefore patients who legitimately require antibiotics, or if this largely reflects over and/or inappropriate use of antibiotics.

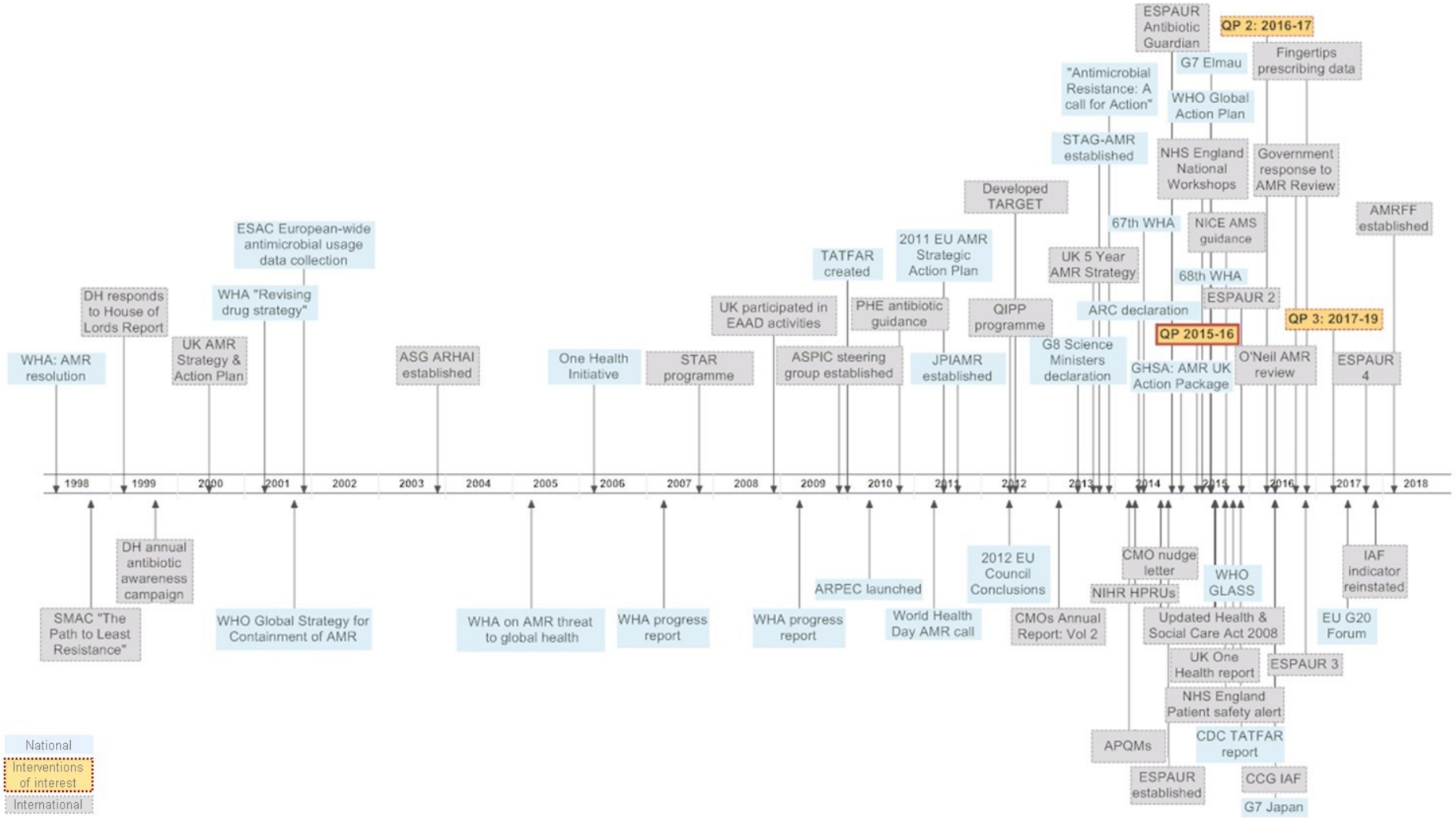
1.3 Stewardship and interventions aimed at reducing antimicrobial resistance

Antimicrobial Stewardship (AMS) is an organisational or healthcare approach aimed at promoting and monitoring the judicious use of antimicrobials to improve patient outcomes and reduce healthcare-associated infections (HCAIs), whilst reducing a rise in antibiotic resistance and preserving the effectiveness of current antibiotics.[53]

The growth in concern around AMR has seen a concurrent evolution of initiatives or public health interventions and the growth of political impetus to take action. AMS has been increasingly promoted, utilising population-level initiatives and policy levers, such as government legislation, economic incentives, educational programmes and public awareness campaigns to name a few, in order to change antibiotic prescribing behaviours and practice, increase knowledge of AMS and ultimately reduce AMR and optimise patient outcomes.[54, 55] In the UK action to date has predominantly been focused on the hospital setting and tackling HCAIs caused by bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*, with development of infection prevention and control (IPC) initiatives and surveillance of HCAIs.[39, 54] Over the past decade with the expansion of scientific evidence, the concept of AMS in the UK has begun to place importance on antibiotic prescribing and AMS in primary care. Figure 1-2 (along with details found in Appendix 1) maps the key AMS interventions implemented which may have impacted primary care antibiotic prescribing in England over a nine-year period, including both national and international guidelines, recommendations and policies. To note these do not include non-health interventions or interventions

not focused specifically on AMR or AMS, which may unintentionally also impact on primary care antibiotic prescribing. The figure serves to illustrate the vast movement in the AMR awareness and governance spheres, with the advancement in multi-faceted approaches over time, and the upsurge in more recent years with greater numbers of interventions implemented concurrently and around the same time period. The cluttered nature of implemented interventions in recent years may make it difficult to identify whether any changes seen in antibiotic prescribing are artefactual, a true exclusive effect of one particular intervention with no confounding caused by others, or a cumulative effect of various simultaneous interventions.

Figure 1-2. Timeline of national and international AMS interventions



1.3.1 Evolution of interventions and the development of AMS in the primary care setting

The threat of AMR and the requirement for appropriate use of antibiotics was highlighted at the 1998 World Health Assembly (WHA) (Figure 1-2, Appendix 1).[56] The following year, the UK government responded to a report entitled "Resistance to antibiotics and other Antimicrobial agents" by the House of Lords Select Committee on Science and Technology, indicating the government's commitment to addressing AMR and the intent to implement a comprehensive strategy, with a range of proposed activities to support it and provide a basis for action plans to be formed from it. The Government's response and subsequent strategy published by the Department of Health and Social Care (previously known as, the Department of Health), took into account the Standing Medical Advisory Committee's (SMAC) recommendations from "The Path of Least Resistance" report and the WHA Resolutions 1998,[57] and proposed addressing AMR through three key components of:

1) strengthening infection prevention and control,

2) prudent antimicrobial use, and

3) generating and implementing surveillance schemes.

Since microorganisms do not recognise geographical boundaries, it was made evident within the UK AMR Strategy, within the series of WHA meetings that have occurred since 1998, and within the 2001 WHO "Global Strategy for Containment of AMR" that surveillance, interventions and collaborations at local, national and international level were imperative. Various steering groups and AMR committees were established, at international and national level, including the Antimicrobial Stewardship subgroup (ASG) for the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) in 2003 and more recently the Joint Programming Initiative in AMR (JPIAMR) (2011) and the WHO convened Strategic and Technical Advisory Group on AMR (STAG-AMR) (2013), to help coordinate research and improve evidence base, promote aligned frameworks, toolkits and data access and shape a global AMR strategy.

These early activities culminated in raising the political agenda around AMR and created the space for action for change with organisations to coordinate this. The 2011 EU AMR Strategic Action plan was developed.[39] This strategy predominantly advocated: a reduction in antibiotic use, making improvements in the appropriate use of antibiotics, infection control, stewardship, and increasing antimicrobial innovation.[37, 58-61] The UK's 2011 annual report from the UK's Chief Medical Officer (CMO) called for action towards preserving antimicrobials,[58] which in turn spurred the publication of the UK's Five Year Antimicrobial Resistance Strategy 2013-18. The five-year healthcare-system-wide strategy is overseen by a cross-government high-level steering group which includes government departments, agencies and devolved administrations. The strategy described three strategic aims, one of which included the requirement to "conserve and steward the effectiveness of existing treatments", with a priority to improve the quality of prescribing in primary and secondary healthcare settings through stewardship.[25, 59, 62]

Successful delivery of the UK five year strategy, or any AMR strategy, would need to engage and involve activity in the human, animal and environmental sectors.[54] The "One Health" approach advocates this and encapsulates the impact of antibiotic use in the human, animal and environmental sectors as well as placing an importance on economic and social components.[54] To address this, the UK Prime Minister commissioned an independent review on AMR in 2014, chaired by Lord O'Neill.[21] The review had an international focus and quantified the future burden and economic impact of increasing drug resistance, it reviewed the role of rapid diagnostics, stimulating the antibiotic pipeline and alternative approaches, the role of agriculture, and the role of infection prevention and control.[21] The findings from this review suggested that a continued growth in AMR would lead to 10 million human deaths globally every year and a reduction in gross domestic product of 2-3.5 per cent (approximately $100 trillion) by 2050.[21]

ESPAUR supplied expertise and data to the Department of Health and Social Care advisory committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infections (APRHAI) in 2014, which

helped to develop Antibiotic Prescribing Quality Measures in England. In 2015, the measures were implemented in the form of a Quality Premium (QP) scheme aimed at responding to the ambitions set by the English government in the UK five-year strategy. The established NHS England QP 2015-16 scheme was financially incentivised to improve patient health outcomes, reduce inequalities in health outcomes, and improve access to health services. The QP incentive comprised a range of elements or targets which were required for reimbursement. One of these was a focus on reducing inappropriate antibiotic use, in particular broad-spectrum antibiotics. The QP differed from other prior or concurrent interventions occurring in England, in that not only was it financially appealing but there was a particular drive to focus on reductions in antibiotic use in the primary care setting. The QP drew on the growing scientific evidence and highlights the primary care setting as an intervention point, using the political and financial spur to push for behavioural change. To support organisations (e.g. general practices, National commissioning groups) in monitoring progress towards the quality improvement goals, National QP dashboards were produced and published annually and since 2016 antibiotic consumption indicators were included within the AMR local indicators profile of Fingertips, a new freely accessible online tool (Figure 1-2, Appendix 1).

Within the same time period as the published QP 2015/16, a resolution for a global action plan to combat AMR was discussed at the 2014 and 2015 WHAs, which was followed by the publication of the WHO Global Action Plan on AMR in 2015, mobilising action at the highest level and across international and global organisations. The international political profile was further raised with the declaration on AMR from the G7 Health ministers (2015). It is important to highlight these clustered interventions, at national and international level, as although this thesis assesses the potential impact of the QP, it cannot exclusively link changes in prescribing behaviour or unintended consequences to the QP alone. Why this intervention differs to others implemented however, has been discussed below.

1.3.2 The Quality Premium, the intervention of interest

England has a publicly funded National Health Service (NHS) which provides health care services to all legal English residents, with most health care services being free at the point of use. Access to the NHS is mainly via referral from a GP in a general practice. GPs are the first point of contact for all initial non-emergency ailments that may or may not require over the counter medication or a referral for further secondary or tertiary care. Within the NHS Structure in England, delivery of medical care is overseen by NHS England and is organised by Clinical Commissioning Groups (CCGs).[25] There are over 200 CCGs in England, which are clinically-led statutory bodies responsible for assessing the local health needs, planning and commissioning the majority of health care for their local populations. Every general practice in England is a member of their local CCG.[25]

In the financial year 2015/16 there were two main quality improvement initiatives in England to reduce antibiotic prescribing, namely the QP and the Commissioning for Quality and Innovation (CQUIN) framework. While the QP was intended to financially reward CCGs, who in turn are responsible for commissioning general practice and primary care, for improvements made to the quality of health services commissioned by that CCG, the CQUIN focused on the improvement in the quality of services and reducing antibiotic prescribing in acute Trusts.[63] In addition to the CCGs main financial allocation for the year, the QP financial incentive would be expressed as £5 per head of population (as a maximum) if all measures were met.[63, 64]

In order to meet the requirements for financial reimbursement the CCGs had six measures to meet, two of which were local agreed priorities. The following were the four national measures outlined:[63, 64]

1. Reducing potential years of lives lost from premature mortality through causes considered amenable to health care (10% of the QP)
2. Urgent and emergency care: with various measures to choose from locally (30% of the QP). One such composite measure included: reducing emergency admissions for acute conditions

that should not usually require hospital admission in adults; emergency admissions for children with lower respiratory tract infection.

3. Mental health (30% of the QP)
4. Improving antibiotic prescribing in primary and secondary care (10% of the QP). This composite measure is made of three parts:
    A. Refers to a reduction in overall antibiotic prescribing for each CCG of 1%, or more, from the 2013/14 values. (This part accounts for 50% of the composite measure);
    B. Focuses on a reduction in broad-spectrum antibiotics prescribing (number of co-amoxiclav, cephalosporins and quinolones as a percentage of the total prescribed), with a required decrease in proportion for each CCG of 10%, or below the 2013/14 England median proportion for 2013/14 (30% of the measure).[63, 64]
    C. Specifies that secondary care providers need to validate their total antibiotic prescription data (20% of the measure).

The 2015/16 QP guidelines reflect a measure to improve antibiotic prescribing in primary and secondary care, with the vast majority of the measure focused on primary care prescribing (80%). Notably, although this measure is focused on reducing antibiotic prescribing, the scheme incentivises reductions of inappropriate prescribing by including other QP measures which safeguard against unintended consequences such as of preventable hospital admissions and mortality (the first two measures mentioned above).

The antibiotic-focused composite indicator specifies the need to reduce broad-spectrum antibiotic prescribing as a proportion of total prescribing in primary care. Broad-spectrum antibiotics should be reserved where possible for the empirical treatment of severe infections which require rapid antibiotic use (i.e. where waiting for diagnostic and antimicrobial sensitivity testing results to guide treatment options would be clinically detrimental) rather than being indiscriminately prescribed for uncomplicated infections in primary care. Reducing the utilisation of broad-spectrum antibiotics in

favour of appropriate narrow-spectrum antibiotics, should decrease the prevalence of AMR and aid in the preservation of the current efficacious antibiotics.

The QP was a repeated annual scheme, with NHS England publishing national QPs to improve antibiotic prescribing each financial year since 2015/16 until 2018/19. The QP for 2016/17 also contained a requirement for CCGs to reduce antibiotic prescribing, but altered the threshold for total antibiotic prescribing to either a ≥4% reduction from the 2013/14 performance or to a level of prescribing equal to or below the England 2013/14 mean performance of 1.161 items per Specific Therapeutic group Age-sex Related Prescribing Units (STAR-PU); the requirement to decrease the proportion of broad-spectrum antibiotics prescribed was maintained at either a 10% reduction or lower, or to reduce the proportion by 20% from each CCG's 2014/15 value.[65] The 2017-19 QP guidance focused on reducing UTI prescribing in primary care and reducing Gram-negative bloodstream infections (BSIs) across the whole health economy.[66]

To assist with implementation of the QP, improve transparency and open access to data, NHS England and the NHS Business Services Authority (BSA) published on a monthly basis an antibiotic QP dashboard freely accessible on the NHS England website. This was intended to be used by CCGs, Commissioning Support Units (CSUs) and NHS England assurance teams to monitor performance against the primary care elements of the QP. PHE later published QP indicator data on an online portal called "Fingertips AMR local indicators".[67] The use of peer comparison as a behavioural intervention has previously been reported to result in lower rates of inappropriate antibiotic prescribing for self-limiting conditions.[68] The increased availability of prescribing data for CCGs and general practices is thought to increase implementation of local surveillance, local audits and feedback to encourage engagement with the QPs.[69]

The system-level implementation, and financial incentive, of this intervention was at CCG level. The mechanisms by which this CCG-level incentive was devised into local measures and targets, and delivered to create behavioural shifts at the general practice-level is thought to have varied between

CCGs and localities, being dependent on CCG-level implementation, demographic population and antibiotic use at the outset. It has been suggested that the use of CSUs (which have specialist skills and knowledge to provide external support to CCGs) and mediated pressure from medicine management teams may play a pivotal role, along with various AMS interventions which were implemented to improve public and clinical knowledge.[70, 71] Medicine management pharmacists are employed within CCGs and their CSUs and are responsible for providing GPs, the predominant primary care prescribers, with prescribing support and advice, including the implementation and monitoring of national prescribing guidelines and the QP scheme.[25] This increased CCG engagement with practices, audits carried out to compare and assess prescribing in practices against national guidelines, and local financial incentives were thought to motivate antibiotic prescribing changes to help meet QP targets.[69] Various interventions were implemented to support the impact of the QP, such as a workshop based around influencing GP prescribing for RTIs and UTIs.[25, 37, 69] The workshop also introduced the freely available TARGET (Treat Antibiotics Responsibly, Guidance, Education, Tools) resources which support the implementation of the QP (Figure 1-2).[61]

Strategies to encourage judicious antibiotic prescribing, such as government reports, patient booklets and clinical practice guidelines, have had varying and somewhat limited success, these have been discussed further below.[13]

1.3.3 Evidence of success in previous AMS interventions

Government-led interventions have been suggested as having a key role in promoting public health, and specifically reducing AMR, by providing a platform for widespread and uniform implementation and clear guidance on compliance and standards.[72] However, the disparity between CCGs and general practice prescribing hints at inconsistent implementation of interventions, perhaps due to a lack of monitoring or because prescribing habits have been embedded in years of experience and are difficult to change.[25] National interventions in the past have been shown to influence the use of antibiotics. In

the UK, revised guidelines in 2006 recommending a reduction of cephalosporin and quinolone prescribing saw a reduction in the use of these broad-spectrum antibiotics and a fall in the incidence of *C. difficile* infections.[73] Guidance, however has not always been adhered to. The National Institute for Health and Care Excellence (NICE) 2008 guidelines for primary care treatment of upper RTIs advised no or delayed antibiotic prescribing.[74] This resulted in a reduction in prescribing for specific upper RTIs, but with a transferal of prescribing to non-specific diagnoses with less stringent guidance, insinuating that practitioners were avoiding diagnoses related to the guidance and had not altered prescribing behaviours.[74]

Other than changes in guidelines, AMS attempts have generally concentrated on national campaigns targeting patient behaviours/antibiotic expectations, or/and on interventions targeting practitioners. There is some evidence of success for both of these approaches. Campaigns targeted at patients have largely relied on posters and leaflet distribution in practices and health centres. However, research on past campaigns targeting patient knowledge and behaviours suggest limited impact on attitudes towards antibiotic prescribing.[75, 76] A survey conducted following a national "Andybiotic" campaign in 1999 (leaflets and materials available at general practices) in the UK, found that only 20% of the public were aware of the campaign, and where recollection was successful, this still led to little impact on patient attitudes and prescription rates.[76] In contrast, a national multimodal AMR campaign (which included print, mass media, website, exhibition, guidelines, seminars) in France between 2002-2004, and cost 22.5 million euros, saw a 21.8% decrease in antibiotic prescriptions per 100 inhabitants compared with the pre-intervention period.[75] It is of note that prior to this intervention France had one of the highest prescription rates globally. Furthermore, changes in prescription rates may have also been attributable to changes in practitioner behaviour, with improved communication contributing to a change in patient perceptions.[75, 77]

AMS interventions which have targeted prescribing behaviours of healthcare professionals have been shown to be effective in trials.[38, 78, 79] Where the interventions had an element of, or were solely

practitioner focused, these were found to be more effective than those focused at addressing patients.[78, 80] Additionally, targeting a change in practitioner prescribing would have a subsequent positive impact on patient perceptions and antibiotic-seeking behaviour.[36] Overall, research suggests that interventions are more effective when they are multimodal and targeted at both the patient and the practitioner, but even more so when they are implemented at system-level using regulatory measures.[36]

As mentioned previously, the use of peer comparison as a behavioural intervention has been shown to successfully reduce rates of inappropriate antibiotic prescribing for self-limiting conditions in a trial completed in the USA.[68] In 2014, a letter from the CMO in England was sent to targeted GPs (those who were in the top 20% of antibiotic prescribers) informing them that their general practice was prescribing antibiotics at a higher rate than 80% of practices in the local area, with action points provided to help them improve the quality of their prescribing (Figure 1-2). The subsequent six months showed a 3.3% decrease in the rate of antibiotic prescribing in those general practices who received the CMO letter compared to a control group.[81] This indicates that tailored feedback and peer comparisons provide an impetus for change. With CCGs appointing medicine management teams to provide feedback and audits to general practices, along with a monthly dashboard and toolkits for comparisons, this should encourage engagement with the QPs.

Governments have different levers which they are able to use to effect change, including the ability to implement regulatory, legislative, service provision and fiscal policies.[82] These are thought to provide greater change than interventions focused on prescriber behaviour change alone.[82] The evidence of the influence of monetary incentives and linking performance to pay was shown with the introduction of the Quality and Outcomes Framework (QOF) in 2004.[83] This was a voluntary annual reward and incentive programme for all general practices in England, rewarding good practice based on numerous indicators. The QOFs were associated with substantial improvements towards targeted clinical outcomes and subsequent quality of care.[83] Evaluations of Pay-for-Performance interventions in other

settings have also been found to be successful at reducing antibiotic prescribing. A Pay-for-Performance and capitation intervention was implemented in Ningxia (rural China) between 2009 and 2012, which led to a 15 percent reduction in antibiotic prescriptions.[84] In Sweden, a Pay-for-Performance scheme found an increased proportion of narrow-spectrum antibiotics being prescribed, i.e. a decrease in broad-spectrum antibiotic prescribing, with no impact on total prescriptions.[79] Notably, the Swedish financial incentives were relatively small, hence it is unlikely that remuneration per se in this instance was what drove the change in prescribing; rather it was more likely that the intervention made the AMR and AMS topic more salient and aided in changing prescribers knowledge and attitudes.[79]

With variation in adherence to AMS interventions and differences in the reported success at lowering antibiotic prescribing levels, the approach required to encourage the acceptance of an intervention by GPs and ascertain implementation is thought to require five themes:

1. permit GPs to reflect on their own prescribing behaviours,
2. decrease uncertainty about management of conditions,
3. improve knowledge on appropriate antibiotic prescribing,
4. facilitate patient-centred care, and
5. be beneficial for GPS to incorporate.[38, 85, 86]

With this said, the QP was implemented with CCG engagement to support and facilitate incorporation at general practice level, with uniform guidance provided through toolkits developed to assist in the improved learning on appropriate antibiotic prescribing as well as guidance on treatment of different conditions, and the ability to monitor and audit prescribing behaviours through new systems and with additional local monitoring via medicine management teams. Interventions can be beneficial to implement in general practices if they decrease workload or if there is perceived financial gain. The QP was financially incentivised and had the political push of being an NHS England-led initiative. Hence, it would be less probable that QP non-adherence would occur as has been seen with other interventions.

1.4 Positive impacts of reductions in prescribing

As antibiotic use acts as a driving force for the selection of resistant bacteria, a reduction in prescribing should theoretically yield a decrease in the prevalence of AMR. The contention is that bacterial strain displacement occurs when the resistant strains can no longer compete in the absence of an antibiotic agent, compared with strains which have other superior traits such as the ability to better colonise.[16]

There is growing evidence that reductions in prescribing of antibiotics are correlated with reductions in AMR in the community,[3] and at the individual patient level, where antibiotic resistance patterns of subsequent infections have been linked to previous antibiotic use.[6] In Iceland and France, resistant pneumococcal isolates decreased following reductions in antibiotic prescribing for children.[16] In the UK a reduction in antibiotic prescribing by general practices was associated with reduced local antibiotic resistance (specifically ampicillin, trimethoprim) over 7 years.[87] A Finnish study found a reduction in macrolide use had an associated reduction of erythromycin-resistant *Streptococci pyogenes* (rates of resistant isolates reduced from 9.2% in 1997 to 7.4% in 2000), with significant declines in regional macrolide resistance and consumption rates.[3, 16, 88]

However, reductions in antimicrobial use have not always lead to reduced resistance. This is perhaps because bacteria become well adapted to the carriage of genes encoding resistance and the resistance determinants might have less impact on microbial fitness than previously thought.[3, 16] Resistance displacement seems to be more difficult when there are multiple resistances, when the resistances are genetically linked and disseminated amongst different strains (e.g. by genes occurring on the same transferrable plasmids) and when antibiotics have been used heavily for an extended period of time.[16] The decline of sulfonamide use in the UK provides an example of where there has been difficulty in displacing resistance. Between 1991 to 1999, the decrease in co-trimoxazole use following English national guidance to preferentially prescribe trimethoprim, did not impact on rates of sulfonamide resistance among *E. coli* isolates.[16]

The prevalence of resistance, although not easily reduced for the reasons mentioned, has been correlated with reductions in prescribing at a national level and in the community. The notion that a decline in prescribing should impact resistance prevalence is plausible, particularly for total antibiotic prescribing and for broad-spectrum antibiotics. Reductions in prescribing should provide to a degree the ability to manage resistance, with the objective of slowing the spread of resistance until new agents are developed.[16]

Widespread inappropriate or unnecessary antibiotic prescribing in the UK has a related unnecessary expenditure to the NHS from prescribing costs. Along with a decrease in resistance, it is thought that reductions in NHS spending on antibiotic prescriptions could also be made, with the annual antibiotic prescription for self-limiting RTIs for adults and children estimated to be close to £3.7 million.[13] The cost savings for the health system from this figure were related to the cost of the drugs alone and did not include costs saved to the individual, or costs due to side-effects (toxicity, consultations and further prescriptions due to diarrhoea, rashes and other adverse reactions). Antibiotic side-effects also commonly include increasing susceptibility to *Candida* and *C. difficile* infection, which would add to the health care costs due to secondary infection and the added duration of recovery.[13]

Research to-date suggests that medicalising with antibiotics at an initial GP consultation encourages patients to revisit when they have similar symptoms, and that the patient would have an expectation of receiving an antibiotic for similar episodes, creating a "cycle of expectation".[13, 36] With every consultation which results in an antibiotic prescription, an expectation is created for subsequent similar symptoms and illnesses, whereby if a patient was prescribed an antibiotic for a sore throat for example, the patient would return to the general practitioner with the expectation of receiving similar treatment for similar symptoms, with the view that treatment with antibiotics would be required for the infection/symptoms to resolve.[13] Reducing antibiotic dispensing at general practices should therefore change these expectations and impact on antibiotic seeking behaviour.[36]

In summary, reducing inappropriate prescribing for self-limiting infections should have a positive impact by decreasing selection pressures for resistant bacteria, expenditure on prescribing and subsequent resistant infections, as well as probable decrease in re-consultations due to changes in patient healthcare seeking behaviour and expectations of therapy.

1.5 Unintended consequences of reduction in prescribing

The QP aims to reduce unnecessary antibiotic exposure, which should conversely ease or slow the rate of AMR. There is however a balance that needs to be made between antibiotic reductions and continued prescribing where appropriate. A reduction in antimicrobial prescribing aimed at ameliorating resistance rates, may be accompanied by a reduction in appropriate therapy. A delay in treatment where antibiotics are required permits bacteria to propagate, which may result in more severe infections or other unintended complications. There are therefore concerns about possible harm to patients where treatment has not been given or is delayed, as an adverse consequence of prescribing reductions.

A 'complication' or 'unintended consequence' of the QP throughout this thesis is defined as a patient who has developed a more severe infection (e.g. community acquired pneumonia, mastoiditis, quinsy, rheumatic fever, scarlet fever, bacteraemia or sepsis) subsequent to the diagnosis of an index uncomplicated RTI, manifested as a consultation in primary care for a more severe infection, a hospital admission for related more severe infection or death.

To date, studies which have assessed this association between levels of antibiotic prescribing and serious complications have found conflicting evidence, and there has not been any systematic synthesis of these findings. Several studies have reported that there is no association between low or decreasing antibiotic prescribing in primary care and bacterial complications following an RTI,[89] while others have reported increases in the incidence of pneumonia,[51] peritonsillar abscess[51, 89] and

subsequent hospital admissions.[13] However, research which reported increases in the incidence of more severe infections reported them as relatively rare events,[51, 89, 90] with certain infections described as not being associated with an increased likelihood of occurring, such as mastoiditis, empyema, bacterial meningitis and intracranial abscess.[51, 89, 90] Other studies have researched whether being prescribed an antibiotic, given a prescription for delayed antibiotics, or not being prescribed antibiotics at all were associated with worsening symptoms and re-consultations, with findings that consultation for new, worsening, or non-resolving symptoms were common regardless of therapy group.[90] The same study also found that being prescribed antibiotics did not reduce subsequent hospital admissions or death for patients with uncomplicated lower RTIs.[90]

Conflicting evidence raises concerns around decreases in prescribing. Although antibiotics may not be indicated for routine prescription at initial primary care consultation, there are perhaps pockets of "at risk" populations, such as vulnerable children, who are at an increased risk of complications due to missed opportunities of earlier diagnosis or therapy. Analogous to the inexorable use of antibiotics, whereby there was a limited evidence base as to the consequences (i.e. resistance), there may be unintended consequences (i.e. serious complications of a bacterial infection) following a decrease in antibiotic prescribing, without robust supporting evidence. Hence, whether an optimal level of prescribing has already been attained, or whether we are able to reduce antibiotic prescribing further without increasing the incidence of infections and complications is not entirely clear.

1.6 Aims and objectives of the thesis

The NHS's scarce resources utilised for meeting the requirements of the QP national scheme should be allocated efficiently to the most effective intervention, and not to interventions which may lead to little or no improvements in the outcomes intended (i.e. reduced antibiotic prescribing) or which may impact negatively on health outcomes (i.e. re-consultations, an increase in the incidence of severe

infections and mortality). Furthermore, it is in the interest of the recipient population that the interventions they receive are effectively improving their health, and that these interventions do not cause unintended harm. This is also of interest to GPs and policy makers who develop and implement these interventions, as evaluations and evidence-based medicine will advise on what works best and would inform current and new interventions and policies.

That said, there is currently limited research into the likely effects of the QP and subsequent reductions in antibiotic prescribing in primary care on patient safety,[33, 91, 92] and no research which quantifies the impact on the temporal trends in relation to specific diagnoses (i.e. uncomplicated RTIs). This thesis aims to examine whether a country wide intervention, specifically the introduction of the 2015-16 QP, which was designed to reduce antimicrobial use in the community had the intended impact of doing so, and whether there was subsequent attributable negative impact on patients safety and outcomes (i.e. increased morbidity and/or mortality). To do this, the focus was on examining the effects in relation to RTIs, as RTIs are the most common clinical indications for consultation in primary care and are the indication most commonly associated with inappropriate antibiotic prescribing.

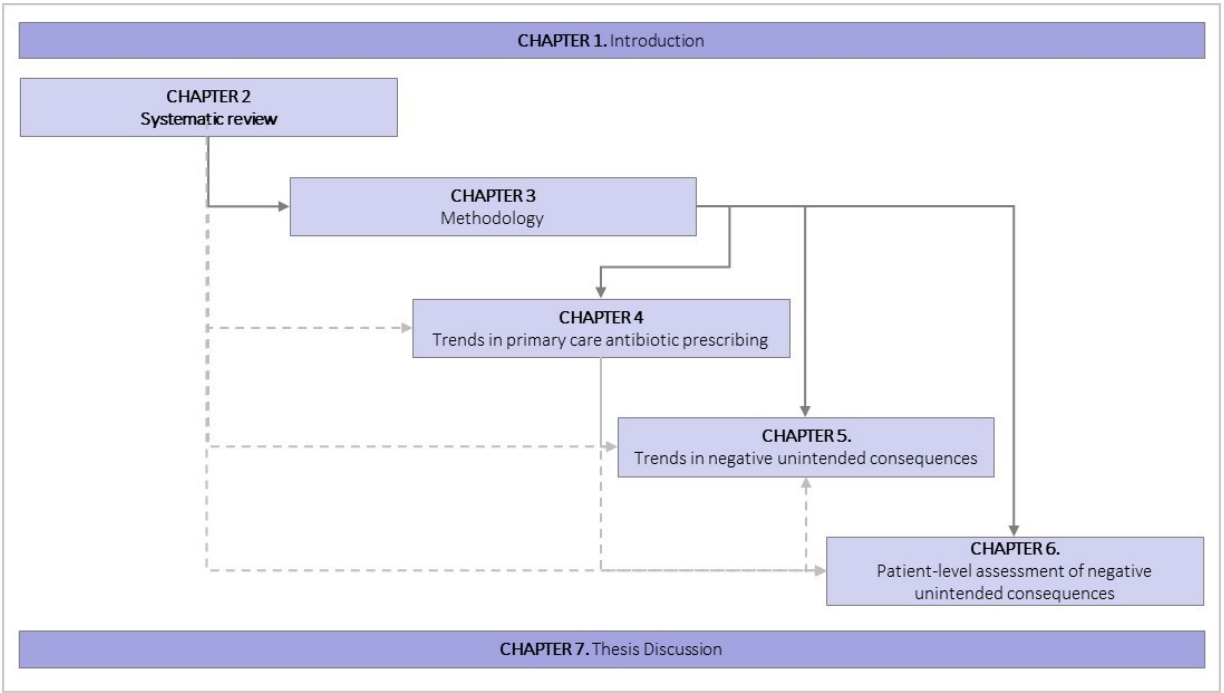
Guidance had already been implemented in previous years to diminish unnecessary inappropriate antibiotic prescribing, hence GPs in England may think that no further reduction in prescribing can be made without endangering their patients' health. Presented with an ill patient along with the difficulties in deciding whether to prescribe (beliefs around patient expectations of an antibiotic prescription, insistent patients, lack of point-of-care rapid testing, the threat of litigation, time pressured consultations) a one-size-fits-all intervention may not always be applicable at individual patient-level care. Whilst the thesis aimed to assess potential complications of the QP, it was imperative to first assess whether the intended reductions in antibiotic prescribing were attained, prior to investigating correlations with any unintended consequences.

The objectives were:

1. To establish whether the QP had impacted on antibiotic prescribing nationally for defined primary diagnoses (RTIs), using national routinely collected healthcare data from the Clinical Practice Research Datalink (CPRD)
2. To use linked routinely collected data to look at the possible adverse impact of reducing antimicrobial prescribing at a national level. To comprehensively look at unintended consequences, subsequent effects were assessed at different health care settings and different outcome severities:
    a. An increase in the use of services, as indicated by returning visits to general practices i.e. re-consultations for unresolved RTI indications
    b. The occurrence of secondary infections, measured by linking patient-level follow-up
        i. consultations for more severe infections in primary care
        ii. hospital admissions for more severe infections
    c. An increase in mortality due to infection

There are six further chapters in this thesis. Figure 1-3 presents the scope of the thesis and how the chapters are linked together to answer the objectives outlined.

Figure 1-3. Thesis overview. Schematic representation of how the thesis chapters relate to each other.

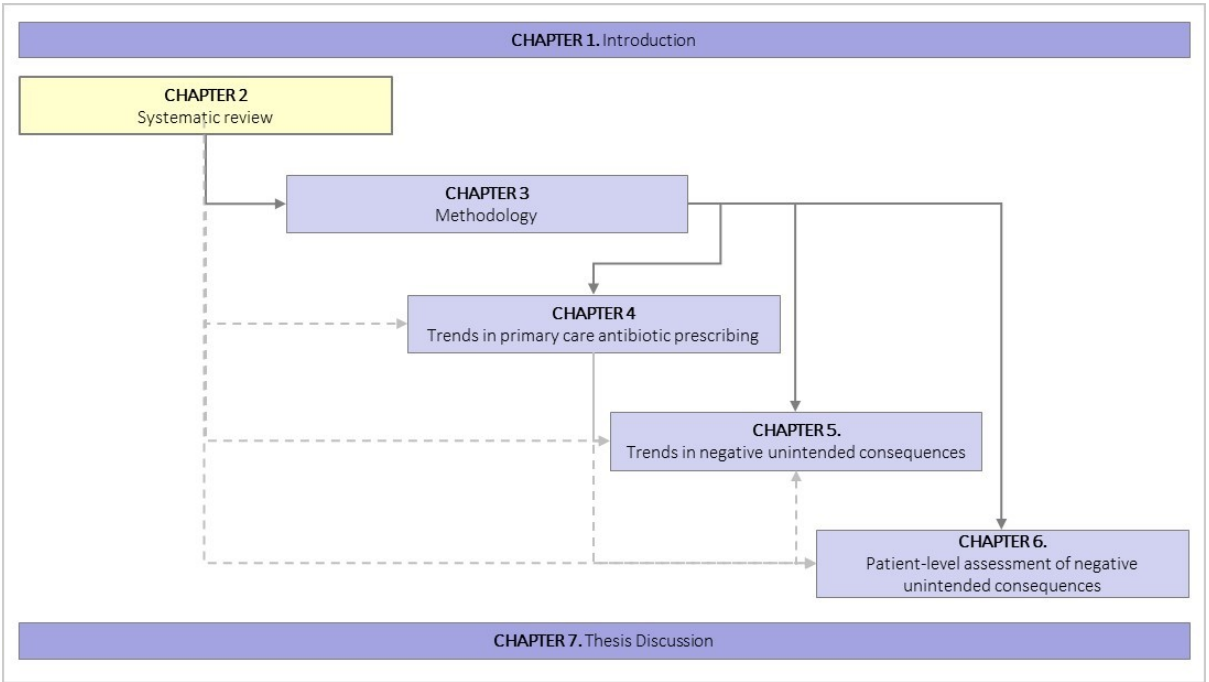


1.6.1 Thesis hypothesis

The null hypothesis is: "Subsequent to the introduction of a national intervention, namely the QP 2015-16, any reduction in primary care antibiotic prescribing in England would not have an associated increase in the incidence of severe infections, assessed either at ecological- or patient-level, indicating that there were no negative unintended consequences following the introduction of the QP".

The alternative hypothesis was, "Subsequent to the introduction of a national intervention, namely the QP 2015-16, a suboptimal reduction in antibiotic prescribing in primary care in England would have an associated adverse unintended consequence, with an increase in the incidence of severe bacterial infections."

CHAPTER 2



Summary:

A systematic review and meta-analysis were undertaken to assess the published evidence evaluating whether patients with RTIs were at increased risk of developing a complication as a result of a lack of timely antibiotic treatment. The review also surmised the ecological impact of a reduction in antibiotic prescribing in primary care on the incidence of RTI complications. The results suggest that patients who had not been prescribed antibiotics had an increased likelihood of developing severe infections, although complications were rare regardless of treatment. The heterogeneity and quality/bias in the studies suggest that larger cohorts and further research are required to improve precision of findings.

Findings from this Chapter, along with the use of a modified Delphi method in Chapter 3, were used to inform on the RTI pathways assessed throughout the thesis (Chapter 4, 5 and 6).

2 SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

2.1 Introduction

The vast majority, at least 80%, of antibiotics are prescribed in primary care.[37, 93] Uncomplicated RTIs are the most common reasons for patients to consult with a GP, and are also the most common indications for empirical antibiotic prescribing in primary care, accounting for approximately 60% of antibiotics prescribed in this setting.[46] Uncomplicated RTIs are a large diverse group of infections, that often and in this research include: upper RTIs, acute cough, sore throat (/pharyngitis), common colds (viral RTIs), sinusitis (/rhinosinusitis), acute otitis media (AOM), and uncomplicated lower RTIs (not including pneumonia).

The reported positive impacts of antibiotic treatments include a reduction in the duration of RTIs and quicker symptom resolution with antibiotic use of between 24 to 48 hours.[94] However, research also suggests that treatment with antibiotics for uncomplicated RTIs often offer minimal benefit as the infections are predominantly of viral origin and self-limiting.[52] Furthermore, antibiotic treatment may instead be associated with negative side effects (including allergic reactions, 'medicalisation' of patients) and toxicity,[51, 95, 96] and will foster the development of AMR through selective pressure on bacterial ecology of respiratory pathogens.[26, 97, 98] Hence, antibiotic use for these common infections is a source of continued debate and much clinical guidance questions the relevance of antibiotic prescriptions for upper RTIs, with recommendations in the UK to either not prescribe or provide a delayed prescription strategy for most patients with upper RTIs (including AOM and acute bronchitis).[46, 51]

Primary care providers continue to over-prescribe for RTIs, with antibiotics being prescribed for approximately 36% of common colds, 40% of sore throat episodes, 70% of AOM (AOM is the most common bacterial infection in early childhood and accounts for 60% of antibiotics prescribed for children[99]) and 90% of sinusitis.[51] This could be due to various reasons, which include: the time-limited

appointments that GPs have, diagnostic uncertainty of the severity of the infection and whether the infection is viral or bacterial,[100] additional pressures placed by expectations and demands of patients,[101, 102] practitioners perceptions of patient expectations, or practitioners anxiety over a serious complication that could occur if an acute bacterial infection were to be missed and the potential for subsequent litigation.[41, 42]

There are clinical concerns regarding complications and progression of bacterial infections where antibiotics have not been prescribed, as an adverse consequence of national antibiotic prescribing reductions.[51, 91] It would be expected that when a national reduction in antibiotic prescribing occurs in primary care, any associated increased risk of complications would most readily be seen in the indications most commonly consulted for, namely RTIs.

2.1.1 Scope of the review

Systematic reviews related to the treatment of RTIs to date provide limited evidence that prescribing prevents complications.[52, 101, 103] Furthermore, when complications have been assessed, they have only been secondary outcomes in the majority of published reviews.[13, 52, 104-107] This systematic literature review aims to assess the evidence and evaluate whether there are findings of adverse outcomes, following a decrease at population-level or an absence at patient-level of antibiotic prescribing in primary care for RTIs.

2.1.2 Objectives

This review appraised the existing evidence to determine whether restricting antibiotics for RTIs in primary care was associated with unintended adverse effects as measured by an increase in clinical complications related to the initial presentation (i.e. increased incidence of complications/progression of index RTIs, increased related hospital admissions or mortality).

i. Patient-level: The primary objective was to quantify the association between previous lack of exposure to timely antibiotics (i.e. no antibiotics) for an acute RTI and patients' risk of developing a clinical complication.

ii. Aggregate-level: The second objective was to describe and estimate the ecological association between a reduction in the rate of antibiotic primary care prescribing and an increase in the incidence of clinical complications subsequent to an acute RTI. This does not necessarily include the assessment of only ecological studies but includes studies where the unit of analysis was not at patient level, e.g. randomised controlled trials (RCT) where general practices were the unit of randomisation and analysis.

2.3 Methods

All methods were undertaken in accordance with the PRISMA guidelines.[108] The review protocol was published on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/). All statistical analyses completed were conducted using Eppi-Reviewer 4.

2.3.1 Search strategy

The search strategy was designed to identify observational or experimental studies investigating the relationship between patients not receiving antibiotic therapy compared to those provided immediate antibiotics, or a reduction in ecological antibiotic prescribing, in primary care for RTIs and the subsequent impact on clinical complications, in any country. The initial search was conducted on the 22nd March 2016 and updated on the 21st July 2016.

The search strategy combined keywords and MeSH terms, using Boolean operators, related to RTIs, primary care prescribed antibiotics and terms related to the outcomes of interest (Table 2-1). The search terms were reviewed by a librarian experienced in assisting with systematic reviews as well as a practicing GP. There were no language or publication date restrictions. The search terms were applied

to the following publication search engines: MEDLINE (1946 to July 2016), EMBASE (+ Embase classic: 1947 to July 2016), and Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 12, 2013, accessed July 2016). Grey and unpublished literature were searched using OpenGrey database (1947 to July 2016). The reference lists of the selected papers and relevant literature reviews were also screened to identify any additional studies not captured by the database searches. All the paper references were exported into EPPI-Reviewer where all the duplicate reference papers were removed prior to the study selection stage. Eppi-Reviewer is a specific systematic review web application, this was used by both reviewers to manage all stages of the review in the same location.[109]

Table 2-1. Example search strategy (Medline)

#	Searches
1	exp Anti-Bacterial Agents/
2	antibiotic*.tw.
3	1 or 2
4	exp Respiratory Tract Infections/
5	exp Pharyngitis/
7	exp Bronchitis/
8	exp Sinusitis/
9	exp earache/ or exp otitis externa/ or exp otitis media/
10	(sore throat or chest infection* or bronchit* or sinusit* or pharyngit* or rhinit* or rhinosinusit* or tonsillit* or laryngit* or croup* or laryngotracheobronchit* or nasopharyngit* or rhinopharyngit* or tracheit* or whooping or pertussis or cough* or coryza* or otitis* or bronchit* or bronchiolit* or pneumon* or pluerisy or otitis* or earache* or respiratory tract infection*).tw.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	(primary care or family practi* or general practi* or hospital admission*).tw.
13	(consequence* or sequela or complication* or secondary infection* or incidence or reattend* or re-attend* or mortality or death).tw.
14	3 and 11 and 12 and 13

2.3.2 Study selection

Titles and abstracts of all potential studies retrieved through the electronic searches were systematically assessed for relevance by two reviewers. Screening used an inclusion and exclusion criteria and was independently completed with detailed reasons for exclusion recorded on a screening

checklist created on Eppi-Reviewer (Appendix 3). The inclusion criteria defined were based on the PICOS framework.[110] Full text papers were obtained for all potential studies identified through the initial screen to enable a further check of study eligibility. Any discrepancies between the two reviewers throughout the study selection was resolved by discussion, and where there was still disagreement a final decision was made through discussion with a third investigator.

Types of studies

Randomised control trials (RCTs), quasi-RCTs, as well as observational (cross sectional, cohort and case-control studies) study designs met the inclusion criteria for studies assessing outcomes at the patient-level. At the ecological level (i.e. unit of observation is the population or community, defined either geographically or temporally) studies which assessed a populations reduction in antibiotic prescriptions were included.

All empirical primary studies were eligible for inclusion. Studies which were not original research or did not provide quantitative data (i.e. those which were not primary studies, were discussion or review articles, guidance or standards related documents, literature reviews, qualitative studies or case reports) were excluded.

Type of participants

Participants/patients of all ages presenting to (or recruited from) primary care with an uncomplicated RTI (upper and certain lower RTIs) prior to the development of a complication. Specifically this includes indications relating to: the common cold, acute sore throat and cough, pharyngitis and tonsillitis, AOM, rhinosinusitis (rhinitis, acute sinusitis), laryngitis and acute bronchitis.[36]

Type of intervention (exposure)

The intervention was the restriction of antibiotic use: either ecologically with a reduction in aggregated antibiotic prescriptions or at patient-level with no prescription given. Studies were excluded if the intervention did not focus on antibiotic prescribing as the intervention or was not related to primary care antibiotic use, e.g. if the antibiotics were for the treatment of severe complications in secondary care. Studies were also excluded if the intervention compared two or more antibiotics and their effects, i.e. studies which compared the effectiveness of antibiotics or were drug review studies.

Type of comparator(s)/control

Where a comparator may have been included: at the ecological-level the comparator would be a population with higher antibiotic use than the intervention group; at the individual-level, the comparator would be participants with immediate antibiotic prescribing rather than delayed or no antibiotic use.

Type of outcome measures

The Primary outcomes assessed were the frequency and severity of infectious complications, i.e. progression or sequelae of infection as a complication of an untreated primary infection, such as cases of mastoiditis following untreated AOM. Studies which detailed counts of subsequent infection in patients prescribed or not prescribed antibiotics were included.

Studies which only assessed symptom resolution of an index RTI were excluded, as were studies which measured infectious complications or outcomes unrelated to primary infections, or unrelated to the intervention of interest, i.e. complications that were related to the use of antibiotics rather than lack of use e.g. diarrhoea due to a *Clostridium difficile* infection, skin rash or vomiting following the use of antibiotics.

Type of setting

Studies were excluded if they were not focused on primary care (i.e. patients who had not been recruited from primary care, or where prescribing was not related to primary care infections). Primary care hospital-based studies were included where either the recruitment of patients was from primary care or the study was for infections which would normally be consulted for in primary care. These criteria were included as it was deemed that comparing patients who present to secondary care is not generalisable to patients who present in primary care with infections that are often less severe, and as the antibiotic prescribing behaviour of interest is primary care-related, any other setting would not be relevant.

2.3.3 Data extraction

Double data extraction was carried out by two reviewers. A designed, pre-piloted, standardised extraction form (purpose-built in Eppi-Reviewer) was used to extract relevant data from the included studies. Two reviewers independently extracted information and cross-checked data for any discrepancies which were discussed and resolved, with a third investigator where necessary. Where two or more studies were found to be using the same data source for the same indications and outcomes in overlapping years, the study with the largest sample size and therefore the most statistical power was used (this occurred in one duplicate data set, two studies).[111, 112] However, duplicate papers which considered different outcomes were assessed separately.

The data extraction tables included the following variables (Appendix 4 contains the full list):

- Study identification details (first author, year of publication)
- Study characteristics: duration (start and end dates), country, study design, study population (demographic [age], number studied overall [N])
- Study methodology/eligibility: main aim, individual- or population-level exposure, Comparator used if any, length of follow-up, details of intervention, antibiotic used, dose and duration

- Extracted outcomes: frequency and severity of unintended consequence, effect sizes if reported, withdrawals and drop-outs. The secondary outcomes collated within the data extraction, but were not required for inclusion, included: re-attendance rates in primary care, whether there was an impact on mortality or excess mortality, and any side-effects.

Details required to identify the risk of bias and assess the quality of the included studies were also collated.

2.3.4 Assessment of risk of bias

The validity of effect estimates calculated from the included studies is dependent on the quality of the study. The quality of a study is conditional on the internal validity i.e. how the study was conducted, analysed and how bias was minimised. To reduce the level of subjectivity when assessing the methodological quality of the included studies, quality assessment tools were utilised, and assessment was completed independently and in a blind manner, by the same two reviewers. The quality of the included eligible observational studies (individual-level studies) were evaluated using the Critical Appraisal Skills Programme checklist (CASP), Oxford UK. As different study designs are susceptible to different biases, the CASP for cohort and CASP for case-control studies were specifically used (www.casp-uk.net).[113, 114] The experimental studies (i.e. RCTs) were assessed using the Cochrane Risk of Bias tool (RoB).[115] The tools used were piloted and tailored where necessary to ensure that the key factors and potential biases related to this review were captured (the amended tools can be seen in Appendix 5, Appendix 6, Appendix 7).

Following assessment, an additional step was taken to produce charts based on a traffic-light system of 'good', 'adequate' and 'poor' reporting as recommended by Cochrane for observational studies (Appendix 5 and Appendix 6).[115] Similarly, the traffic-light system was completed for the assessments undertaken using the RoB tool.

2.3.5 Data synthesis

The primary outcome measure was development of complications following an initial uncomplicated RTI, with the outcome measure being a calculated odds ratio (OR). The OR describes the ratio of the odds of events occurring in the group of participants who were not given antibiotics compared to the odds of events occurring in the group of participants who were prescribed antibiotics (these being the controls or comparators). Explanations of and the calculation used to obtain the OR and 95% confidence intervals have been detailed in Appendix 8. The OR cannot be calculated where there were no events in one of the groups, as is customary in these instances a value of 0.5 was added to the empty cells of the 2x2 OR table.[116, 117] Where no events were found in both groups, the study results would provide no additional information about the relative probability and therefore were omitted from the meta-analysis (described below).[117] These studies would continue to contribute to the findings in that the risk difference in such situations would be zero.

The secondary outcome was to assess complications reported in studies at an aggregated level. A narrative descriptive synthesis was completed on the associations found in this subset of included studies. No further analysis was completed on these studies as it was presumed they would be too dissimilar (in the outcomes assessed, settings, study designs and biases to name a few) for statistical pooling of estimates and comparison.

Meta-analysis

Pooling results and combining comparative studies in a meta-analysis provides increased numbers of participants, reduces random error and narrows the confidence intervals, which increase the power and precision in estimating a statistically significant intervention effect.[117]

Following the calculations of summary statistics for each included study (ORs), an overall pooled treatment effect was calculated as a weighted average of the ORs reported in each study.[117] The weights used are a reflection of the amount of information that each study contains, usually calculated

as the inverse of the variance (i.e. the square of the standard error) of the OR, hence is closely related to and impacted by the sample size of the study.

As a meta-analysis investigates the treatment effect across numerous primary studies, the included studies are assumed to be conducted in a similar manner, although there will of course be variation in the participants or patient groups included, the settings, or the methods of delivery of the intervention (i.e. which antibiotics are used, dosage, timing etc.). Whilst it is expected that some variation in the results across the studies assessed will occur due to chance, the treatment effect may also vary due to these differences in study characteristics. To assess the possibility in excess variability between the results of different studies, the X^2 (Chi-squared) test and the I^2 statistic were used to test for heterogeneity (Appendix 9), along with the visual examination of the forest plots (poor overlap between study confidence intervals is suggestive of statistical heterogeneity). The significance level for the X^2 test was set at 0.1. The I^2 statistic indicates the proportion of total variability which can be explained by heterogeneity, the effect of which was regarded as moderate where I^2 was above 50% and considerable if above 75%.[115] Where heterogeneity was moderate-to-considerable, a random-effect meta-analysis, described by DerSimonian and Laird, was performed.[115] This was decided as a better model over the fixed-effects model as it incorporates the assumption that the different studies are estimating different, yet related treatment effects (i.e. assumes that the true treatment effect for the individual studies vary around an overall treatment effect, rather than each study having a "fixed" same value and differences being solely due to chance as is the case with fixed effect meta-analysis), and includes within- and between-study variability into the analysis (i.e. study weights are based on a combination of their own variance and the between-study variance).[115, 117]

Analysis of subgroups or subsets

Different study designs were assessed in a subgroup analysis to accommodate for variation in the outcome effect due to heterogeneity in study design. Subgroup analyses were also completed to assess

the differences in outcomes across different age groups. Doing so by dividing studies based on study level characteristics (e.g. recruitment or inclusion of participants based on age) or participant data (where participant level characteristics and age groups were provided within the study). This would permit the indirect comparison between the subgroups within the population and identify whether the effect of the intervention was the same with different age groups.

Sensitivity analysis

Sensitivity analyses were performed to assess the degree to which results were influenced by the following, and where heterogeneity existed to try and account for this variation by:

- Publication year: removing studies carried out prior to 1980. Older studies reflect a time when index uncomplicated RTI rates were different, population incidence was higher and the course of RTIs were unlike present day, in that complications were not as rare. The basis of treatment and the impact of antibiotics would therefore be expected to vary when compared to more recent study findings.
- Index lower RTIs: Where the index uncomplicated RTI assessed was a lower RTI this may be more highly associated with complications compared to upper RTIs. To assess whether this impacts the pooled effect measure, any studies assessing complications following an index lower RTI were removed.

Publication bias

Publication bias arises when manuscripts are, or are not, published based on their direction or significance/strength of the study findings.[118] This review searched for studies in the grey literature in an attempt to identify any studies which may not have been published for this reason. Studies were also not excluded based on language. Any residual publication bias was assessed using a funnel plot

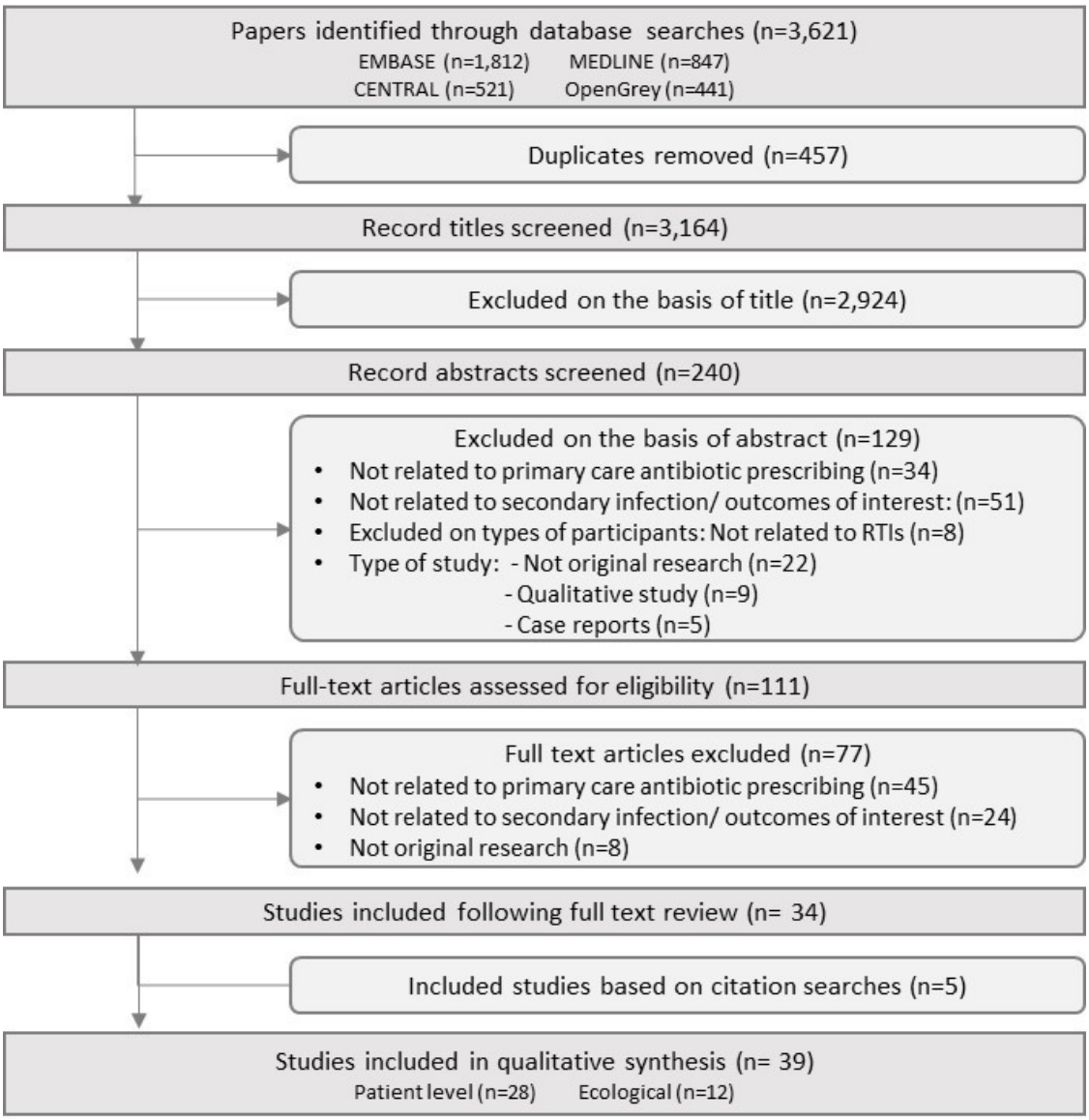
(scatter plot of OR plotted against Standard Error). Other than publication bias, potential asymmetry could also be caused by heterogeneity, reporting bias and chance.[119]

2.4 Results

2.4.1 Search strategy results

The electronic database searches retrieved 3,621 records, of which 2,924 were discarded based on their titles (Figure 2-1). A total of 240 abstracts were independently screened by two reviewers and out of these, 129 studies were excluded on the basis of their abstract not meeting the eligibility criteria, predominantly due to studies not assessing further progression of an RTI into a complication (n=51). The remaining 111 full-text papers were assessed in full for eligibility by the two reviewers. Of these, 77 were excluded and a total of 28 patient-level studies were included in the review,[94-96, 99, 100, 111, 120-141] with an additional 12 ecological-level papers (of which 1 was also included in the patient-level analysis).[51, 139, 142-151]

Figure 2-1. PRISMA flow chart depicting exclusion and inclusion of studies into the systematic review



2.4.2 Description of included patient-level studies

It was assumed that the review would unintentionally yield itself more to observational studies due to the ethical questions which may arise where antibiotics are not provided as they could potentially be beneficial to the recipient participants. In practice however, out of the 28 studies included, 17 (61%) were RCTs,[94-96, 99, 100, 111, 120-123, 128, 132, 134, 135, 137, 138, 141] nine cohort studies (four of which were prospective cohort studies), [124, 127, 129-131, 133, 136, 139, 140] and two case-control studies (Table 2-2). [125, 126] All the studies

were completed predominantly in European countries (n=27, 17 of which were in the UK and six in the Netherlands), with only one study setting outside of Europe, in the USA.

Included studies were published between 1956-2014. There were no marked temporal trends in the years that these were published, apart from a lack of published eligible studies between 1960-1980. There was also a slightly increased number of published eligible papers in 1997, with two RCTs published in the UK and two observational studies in the Netherlands. All analysed data from different sources and data spanning different time periods. The majority (82%) of studies were conducted in the 1990s or 2000s (n=13 and n=10 respectively). Six studies were conducted pre-1980, with one study dating back to the 1950s, during which time the rates of serious complications were much higher than present day, although the findings do not suggest any outliers or drastic differences in the odds of complications found pre-1980s.

The included studies investigated a total of approximately five million patients, either through registered patients in a primary care database or patients recruited into the studies (Table 2-2). The sample size varied from 10 to more than 1.5 million, with the larger studies generally being observational in design and smaller studies RCTs (Table 2-2, the largest RCT was n=670). The age of participants ranged from 3 months to 65 years where defined, although various studies, particularly those which utilised databases did not apply an age restriction and could have included younger or older patients.

Many of the studies in the review recruited patients based on symptoms of a sore throat (n=10, with two further studies based on a combination of sore throat and other index diagnoses such as AOM, 36%) (Table 2-2). The other common diagnoses for inclusion of patients were for symptoms of AOM (n=6, with one additional study assessing primary AOM and other index uncomplicated diagnoses). Winchester *et al.* (2009) focused on index lower RTIs,[140] which may be associated with increased complication outcomes, while two further studies included lower RTIs in combination with other upper RTI diagnoses.[125, 133]

The antibiotics used within the studies, where specified (17 studies), were predominantly penicillins (penicillin, penicillin-V, amoxicillin, fenticillin, phenoxymethylpenicillin), with the only exception to that being a study assessing tetracycline (doxycycline) for sinusitis diagnoses (Appendix 10 for further details).[134] Where antibiotic treatment was specified, administration of these drugs would have been orally, apart from one study (1950s) which administered intramuscular penicillin.[127] Ten studies did not specify the antibiotics prescribed or provide details regarding dose and duration. These studies either utilised primary care databases or were observational studies where there would not have been one set antibiotic treatment. These studies did not compare the effect of one antibiotic treatment type but the effect of an antibiotic strategy (i.e. whether an antibiotic was prescribed or not).

Antibiotics were not provided on the basis of bacteriological results but clinical judgement for all apart one study by De Meyere *et al.* (1992), where recruitment criteria specified the inclusion of only patients with a positive culture for Group A Beta-haemolytic streptococci.[152] Dagnelie *et al.* included patients with an acute sore throat with a moderate chance of Group A Beta-haemolytic streptococci, whereby participants had to meet three out of four criteria (history of fever; anterior cervical lymphadenopathy; tonsillar exudate; and absence of cough).[95] Participants in these two studies may have been more likely to benefit from antibiotic prescribing and more prone to complications.

Of the 28 included studies, only 10 assessed the association of antibiotic prescribing with the risk of developing a more severe infection as the main objective (Appendix 10).[94, 124-126, 129, 131, 133, 136, 139, 140] The remaining 18 studies, although reporting on whether complications occurred, had primary objectives focused on identifying the impact of antibiotics on symptom control/resolution and recovery from illness. Hence, in less than half of the papers the study design was not constructed around identifying the primary aim of this review.

Table 2-2. Characteristics of individual-level included studies

Study	Study design[a]	Country	Study duration	Primary aim	Age group[b]	Index infection	Complications assessed	Number of participants	Intervention/ Exposed (No antibiotics) n/N	Non-exposed (Antibiotics) n/N	OR	95% CI	SE
Autret-Leca (2002)[94]	RCT	France	3m in winter 1998-99, 6m in winter 1999-2000	Yes	C	Sore throat	Acute otitis media	203	16/99	10/104	1.81	0.78 - 4.21	0.43
Bucher (2003)[100]	RCT	Switzerland	Nov-Apr of 1997 - 2001 (4 winter seasons)	No	A	Rhinosinusitis	Brain abscess	252	1/127	0/125	1.98	0.07 - 59.68	1.74
Chapple (1956)[120]	RCT	UK, England	Feb 1954 - Sep 1955	No	G	Sore throat	Acute otitis media	283	1/97	5/186	1.97	0.56 - 6.97	0.65
Dagnelie (1996)[95]	RCT	The Netherlands	1990 - 1992	No	C & A	Sore throat	Quinsy	239	2/118	0/121	4.17	0.19 - 93.50	1.59
De Meyere (1992)[152]	RCT	Belgium	1989	No	C & A	GAHBS pharyngitis [c]	Rheumatic fever*	173	0/91	0/82	-	-	-
De Sutter (2002)[122]	RCT	Belgium	Oct 1998 - Dec 1999	No	A & E (C>12y)	Upper RTI and rhinosinusitis	None observed*	408	0/206	0/202	-	-	-
Howe (1997)[123]	RCT	UK, England	Oct 1993 - May 1994	No	A	Sore throat	Quinsy	154	0/54	1/100	0.92	0.03 - 27.77	1.64
Little (1997)[96]	RCT	UK	Sep 1994 - May 1996	Yes	G	Sore throat	Otitis media, sinusitis, quinsy	670 [d]	3/434	2/236	0.81	0.14 - 4.91	0.92
Little (2014a)[128]	RCT	UK	Mar 2010 - Mar 2012	No	G	Acute RTI	Otitis media, sinusitis, pneumonia, quinsy, cervical adenitis, meningitis or septicaemia	448	3/122	8/326	1.00	0.26 -3.84	0.69
McCormick (2005)[99]	RCT	USA, Texas	May 2000 - Mar 2003	No	C	Acute otitis media	Mastoiditis*	209	0/100	0/109	-	-	-
Mygind (1981)[132]	RCT	Denmark	Nov 1977 - Apr 1978	Yes	C	Acute otitis media	Mastoiditis	149	0/77	1/72	0.46	0.02 - 13.95	1.74
Stalman (1997)[134]	RCT	The Netherlands	Sep 1993 - Aug 1995	No	A	Upper RTI	Sinusitis*	192	0/94	0/98	-	-	-

Study	Study design[a]	Country	Study duration	Primary aim	Age group[b]	Index infection	Complications assessed	Number of participants	Intervention/ Exposed (No antibiotics) n/N	Non-exposed (Antibiotics) n/N	OR	95% CI	SE
Tahtinen (2011)[135]	RCT	Finland	Mar 2006 - Dec 2008 (excluding Jun and Jul)	No	C	Acute otitis media	Mastoiditis, pneumococcal bacteraemia, pneumonia ^	319	2/158	0/161	4.13	0.18 - 92.26	1.59
van Buchem (1981)[137]	RCT	The Netherlands	Jan - May 1979 and Oct - Mar 1980	Yes	C	Acute otitis media	Mastoiditis*	87	0/40	0/47	-	-	-
van Buchem (1997)[138]	RCT	The Netherlands	Mar 1993 - Mar 1994	No	G	Acute maxillary sinusitis	None observed*	214	0/106	0/108	-	-	-
Zwart (2000)[111]	RCT	The Netherlands	1994 - 1996	No	A	Sore throat	Peritonsillar abscess	561	3/177	0/384	13.22	0.66 - 265.76	1.51
Zwart (2003)[141]	RCT	The Netherlands	1994 - 1996	No	C	Sore throat	Streptococcal complication	156	8/56	3/100	5.39	1.37 - 21.23	0.70
Fry (1958)[127]	PC	UK, England	1955 - 1957	No	G	Acute tonsillitis	Quinsy, acute nephritis	405	0/360	3/122	0.06	0.00 - 1.11	1.53
Howie (1985)[124]	RC	UK, Scotland	1976 - 1979	Yes	C	Sore throat	Rheumatic fever	10 [e]	1/66,000	9/264,000	0.44	0.06 - 3.51	1.05
Little (2014b)[129]	PC	UK, England and Wales	Nov 2006 - Jun 2009	No	A & E	Sore throat	Quinsy, sinusitis, otitis media, cellulitis or impetigo	10,286 [f]	73/4,536	75/5,750	1.24	0.89 - 1.71	0.17
Marchetti (2005)[130]	PC	Italy	Feb - Mar 2001	No	C	Acute otitis media	Mastoiditis*	1,277	0/743	0/84	-	-	-
Meropol (2013)[131]	RC	UK	Jan 1985 - Dec 2006	Yes	A & E	acute RTI	Pneumonia	814,283	116/528,969	180/1,002,050	1.22	0.97 - 1.54	0.12
Petersen (2007)[133]	RC	UK	July 1991 - Jun 2001	Yes	G	Otitis media, sore throat, upper RTI and chest infection	Mastoiditis, quinsy, pneumonia [g]	>1.5 million	3,454/920,027	5,823/2,435,326	1.57	1.51 - 1.64	0.06
Taylor (1983)[136]	PC	UK, Scotland	1976 - 1979	Yes	C	Sore throat	Acute nephritis	39 [h]	21/60,000	18/240,000	4.67	2.49 -8.76	0.32
Thompson (2009)[139]	RC	UK	Jan 1990 and Dec 2006	Yes	C	Acute otitis media	Mastoiditis	464,845	149/389,649	139/792,623	2.18	1.73 - 2.75	0.12

Study	Study design[a]	Country	Study duration	Primary aim	Age group[b]	Index infection	Complications assessed	Number of participants	Intervention/ Exposed (No antibiotics) n/N	Non-exposed (Antibiotics) n/N	OR	95% CI	SE
Winchester (2009)[140] [i]	RC	UK	Jan - Dec 2004	Yes	G	lower RTI [j]	Pneumonia and hospital admitted LRTI	151,088	514/21,316	633/128,539	4.99	4.44 - 5.61	0.06
Crocker (2012)[125]	CC	UK, Wales	Dec 2008 - Feb 2010	Yes	C	URTI, LRTI or cough	Pneumonia, empyema	255	58/139	31/114	1.92	1.13 - 3.27	0.27
Dunn (2007)[126]	CC	UK	1995 - 1997	Yes	G	Sore throat, pharyngitis, tonsillitis	Quinsy	940,928	23/30,336	169/167,980	0.75	0.49 - 1.16	0.22

[a] Study design: RCT - Randomised Controlled Trial; PC - Prospective Cohort, RC - Retrospective cohort, CC - Case-Control

[b] Age Group: C - Children; A - Adults; E - Elderly; G - General Population

[c] The only study included in the review which only included RTI patients with distinguished bacterial aetiology; patients with a positive culture for Group A Beta-haemolytic streptococci were included in the study

* No complications were observed. Cells highlighted in grey to distinguish

^ No mastoiditis cases were reported as a complication

[d] Data could not be separated between those who were not prescribed antibiotics and those who were prescribed delayed antibiotics. The exposed group in this instance includes combined no antibiotics and delayed antibiotics

[e] Denominator used were estimated and not the number in the cohort. The included number of patients not clear in this study due to estimates used.

[f] Count is of patients who were in the immediate or no antibiotic group, delayed antibiotic group was not included here

[g] Study attempted to assess acute rheumatic fever and acute glomerulonephritis following a sore throat, however, could not distinguish between chronic and acute events and were virtually no cases of either

[h] Denominators were based on assumptions and not actual counts of sore throat consultations

[i] The only study included which assessed index infection of lower RTI only, all others were upper RTI related (including acute otitis media). Petersen (2007) and Crocker (2012) included lower RTIs along with upper RTIs. Highlighted row to distinguish

[j] Index infection was not an upper RTI. Vast proportion (53.5%) of hospital admissions were on the same day as index consultation

2.4.3 Results of individual-level studies and the unintended consequences identified

Of the 28 patient-level studies included in the review, seven papers (25%) reported no complications occurring in either groups, i.e. in those prescribed and those not prescribed antibiotics (the rows presenting these studies have been coloured in grey in Table 2-2).[99, 121, 122, 130, 134, 137, 138] The remaining 21 studies, which reported cases of RTIs developing into a subsequent more severe infection where antibiotics were withheld, were included in the meta-analyses. A total of 11,558 complications were reported, comprising 4,448 in patients who were not given antibiotics and 7,110 who were given antibiotics (notably the antibiotic groups often contained a larger number of patients in that arm, therefore this is not reflective of an increased risk or odds in this group). Of the complications reported, quinsy and mastoiditis were the most frequent, having been either specifically assessed or appearing as a complication (in eight and seven studies respectively) (Table 2-2). Pneumonia or empyema (5 studies), AOM (5 studies) and sinusitis (4 studies) were also commonly reported complications (Table 2-2).

Of the odds ratios (OR) calculated where complications had occurred, 50% of included studies (14/28) reported complications which equated to ORs greater than one (ranging from 1.22 to 5.39, with an anomalous OR=13.22 from the Zwart *et al. (2000)*[111]),[94, 95, 100, 111, 120, 125, 129, 131, 133, 135, 136, 139-141] i.e. the majority of studies indicated a greater odds that patients with index uncomplicated RTIs develop complications when the patient was not prescribed an antibiotic, compared to the odds of developing a complication had the patient been prescribed an antibiotic. This can be visually seen in the forest plot as many of the study effect measurements are located favouring the control (controls in this review being those who were prescribed antibiotics) (Figure 2-4). Six of the included studies (21%) favoured the intervention (not being prescribed an antibiotic), with these OR being less than one (ranging from 0.06 to 0.92), suggesting that patients do not experience benefits from antibiotic treatment.[96, 123, 124, 126, 127, 132] One study had a calculated OR value of 1, which indicates that the estimated effects are the same in both groups, and that not being prescribed an antibiotic did not affect the odds of developing a complication.[128]

Although half of the studies suggest that the odds of developing a complication is higher for patients who are not prescribed an antibiotic, a key finding throughout was that these events were extremely rare in both groups (those not prescribed and those prescribed antibiotics) (Table 2-2). The forest plot also presents OR confidence intervals (CI) which are predominantly large, with seven extremely large CIs, suggesting that the level of precision is low in these studies. Furthermore, the CI for 15 (71%) of the 21 studies where OR were calculated include the value of one. The meta-analysis below assesses further.

2.4.4 Other findings of individual-level studies

Number Needed to Treat

The number needed to treat (NNT) is an epidemiological measure used to communicate the effectiveness of a particular medication or intervention, specifically for this review the calculation would be the average number of patients who would need to be treated with antibiotics to prevent one additional complication. Five studies calculated the NNT with respect to patients developing a complication: Autret-Leca *et al.* (2002) estimated that 94 children with sore throats needed to be prescribed antibiotics to avoid 6 cases of AOM.[94] Little *et al.* (2014b) calculated that to avoid one complication (of quinsy, sinusitis, otitis media, cellulitis or impetigo) 193 patients with sore throats need to be prescribed an antibiotic,[129] while Petersen *et al.* (2007) Thompson *et al.* (2009) and Winchester *et al.* (2009) reported the greatest NNT: with 4000 episodes (of otitis media, sore throat, upper RTI or chest infection), 4831 (of AOM), and 1002 (lower RTI), needing to be treated with antibiotics to prevent one complication (mastoiditis, quinsy and pneumonia; mastoiditis; pneumonia and hospital admissions for lower RTIs) respectively.[133, 139, 140]

Symptom duration and resolution

Various studies primarily focused on the mean duration of index infection/related symptoms and the time required for resolution, with the hypotheses being that antibiotics would improve and reduce the

time to symptom resolution. What was observed in three studies however, was that symptom resolution was unrelated to treatment method (i.e. antibiotics versus placebo), although it should be noted that Tahtinen *et al*. (2011) did state that treatment with antibiotics improved fever, appetite, irritability and decreased activity.[135, 137, 141]

Where studies reported that symptoms persisted greater in one group compared to another, this was in reference to mainly minimal differences. Patients experienced an accelerated recovery of one or two days when treated with antibiotics compared to placebo in six studies, with the number of days till recovery varying between four to six.[95, 100, 111, 127, 134, 152] Dagnelie *et al*. (1996) found patients to have improved symptoms within two days of starting antibiotics, however further assessment revealed that this effect and a significant difference was only found in patients with a positive culture for Group A Beta-haemolytic streptococci.[95] De Sutter *et al*. (2002) found a much greater difference, with rhinorrhoea duration significantly shortened by 5 days with antibiotic use,[122] with two further studies suggesting a decrease in pain and symptoms for patients treated with antibiotics compared with placebo.[132, 138]

Reoccurrence and re-consultation

Administration of antibiotics made no difference in the relapse or number of recurrences in three studies.[111, 131, 137] However, two studies suggested that re-consultations with new or unresolved symptoms were less common in patients prescribed antibiotics.[100, 129] Contrary to this, a larger number of studies found that reattendance and relapses with symptoms and new episodes occurred more often in patients who were treated with antibiotics rather than placebo/no antibiotics;[96, 99, 138, 141] in three of these studies the differences were not negligible: McCormick *et al.* (2005) found that 36% of immediate-antibiotic (n:12/33) patients had recurrences compared with 17% (n=12/71) in those who did not receive antibiotics.[99] Similarly van Buchem *et al.* (1997) found that 21% of patients treated with antibiotics and 17% with placebo had a relapses. Dagnelie *et al.* (1996) assessed participants who had

harboured Group A Beta-haemolytic streptococci and found that 17.9% (10/56) treated with antibiotics and 10.9% (6/55) with placebo had a reoccurring infection.[95]

Other complications reported

Gastrointestinal symptoms, specifically diarrhoea was a complication frequently reported as significantly more likely in the antibiotic group, often only reported as a side effect in patients taking antibiotics.[100, 122, 132, 138] Subjective symptoms such as dysphagia, itching, abdominal pain and nausea were also reported more frequently with patients who were given antibiotics.[111, 152] One study reported no differences in the incidence of skin rashes, abdominal pain or vomiting,[122] with another study finding a correlation between the occurrence of skin rashes following antibiotic use (including a case of exanthema; a skin rash accompanying disease or fever).[132]

A concerning complication reported by Tahtinen *et al.* (2011) following antibiotic use was a patient (child) whose nasopharyngeal sample identified an antimicrobial resistant isolate of *Streptococcus pneumoniae*. Importantly the initial sample had shown intermediate resistance which later had developed to full resistance to penicillin.[135]

2.4.5 Risk of bias within studies

All 28 included papers were assessed for the strength of the evidence reported by evaluating the methodological quality (Figure 2-2 and Figure 2-3). Appendix 5, Appendix 6 and Appendix 7 provide the appraisal tools used along with additional information for each heading shown in Figure 2-2 and Figure 2-3.

Studies generally described the methods used well, as well as the inclusion criteria and baseline characteristics of participants. Although descriptions were provided, several studies described selection biases, including Little *et al.* (2014b) who stated that the patients who were prescribed antibiotics significantly differed to those who were not given antibiotics in several characteristics

(particularly fever, pus and severity of inflammation), many of whom would have been more likely to have a progression to a complication and would have confounded the effects seen.[129] Crocker *et al.*(2012) also outlined that the duration of index illness was shorter in patients not prescribed antibiotics.[125]

The included studies predominantly utilised multi data collection methods (Appendix 10) including primary care consultations, self-reporting tools such as diaries or questionnaires, telephone follow-ups, while 17 studies used a combination of such tools to gather information, and seven studies engaged the use of recorded information from database or register sources only (Appendix 10). Using a questionnaire or self-reporting tools to collect data may introduce bias as not all participants may have permanent addresses, may not have a high understanding of the language within which the study was carried out, or those likely to respond may have different characteristics to those who did not. Using multimodal methods such as a follow-up telephone call where responses were not received, or a follow-up consultation, aimed to counteract this selection bias in the design of several studies.

Certain studies however included their own unintentional sources of selection bias, as with Chapple *et al.* (1956) who excluded participants for socio-economic reasons and where the treatment was not adhered to adequately. This poses questions around how representative the participants were and measurement bias in that in a normal setting, certain patients may not follow through in obtaining antibiotics prescribed, and may not adhere to doses or duration when prescriptions are cashed in. Furthermore performance and selection bias would have also been introduced in the Chapple *et al.* (1956) study as participant recruitment occurred when the physician had decided that the pressure of work would not prevent the process required for the trial; this may have been in the periods of the year when infection and antibiotic prescription rates were lower, when complications were rarer, and may not be generalisable to a usual primary care setting.[120] Figure 2-2 displays the difficulties in quality and bias also prevalent in the other older studies.[124, 127, 136, 137]

Several studies (n=17, 4 of which were observational studies) attempted to control for confounders by excluding patients who had serious underlying medical conditions or chronic disease (such as: cystic fibrosis, severe immune deficiencies, cerebral palsy, diabetes mellitus, chronic lung disease).[94-96, 99, 120, 122, 123, 125, 128, 130-132, 134, 135, 140, 141, 152] These patients are likely to be treated differently under normal conditions in primary care, antibiotics may often be prescribed and required as comorbidities might impair immune competence and physicians deem these patients to be at a higher risk of developing a complication. Attenuating for patient risk factors and characteristics is less of a concern with RCTs where participants are randomised, however for the majority of the observational studies this was not addressed. Residual confounders, regardless of design, remained within several studies that either selected populations at higher risk of complications or did not sufficiently account for confounders within analysis; for example Autret-Leca *et al.* (2002) selected patients who had a history of repeated occurrences of AOM and who were more at risk of developing complications.[94] Bucher *et al.* (2003) also recruited patients with greater severity in symptoms and those who had a history of repeated rhinosinusitis.[100] Likewise, Chapple *et al.* (1956) only included patients whose symptoms were of severity that they would be given antibiotics, and Little *et al.* (2014a) stated that those who were prescribed antibiotics had slightly more severe symptoms.[128] All of these studies were prone to confounding by severity.[120, 153]

In order to ensure that outcomes detected were related to the index infection assessed in the studies and that any complications or effects of antibiotics reported were due to the influence of treatment rather than the initial severity of the infection, 13 studies excluded patients with complaints or symptoms that had persisted for some time prior to recruitment, in this way attenuating misclassification and detection bias where complications and outcomes would be more imminent in these patients: Autret-Leca *et al.* (2002) excluded participants who had symptoms for more than 5 days prior to consultation,[94] Bucher *et al.*(2003) 4 weeks,[100] Dagnelie *et al.* (1996) 14 days,[95] De Sutter *et al*. (2002) 30 days,[122] Stalman *et al.* (1997) 3 months,[134] van Buchem *et al.* (1997) 3 months,[138] De Meyere *et al.* (1992) 5 days,[152] Little *et al.* (2014b) 14 days,[129] Dunn *et al.* (2007) 30 days,[126] Marchetti

et al. (2005) 36 hours,[130] Zwart *et al.* (2000) 7 days,[111] Zwart *et al.* (2003) 7 days.[141] Notably the durations differ markedly from 36 hours to 3 months, and whether the shorter durations account for a long enough time or whether 3 months is too long a duration and hence introduces detection bias is uncertain.

Two studies attempted to reduce misclassification bias by excluding patients who had outcomes recorded on the same day as the index consultation, as any such outcomes would not necessarily be associated with the treatment.[126, 133] Similarly, to reduce detection bias, several studies excluded participants who had previously been exposed to antibiotics, in the preceding 2 weeks,[94, 123, 137, 152] or 1 month/4 weeks,[95, 100, 122, 132, 134, 135] while Marchetti *et al.* (2005) did not specify a duration although stated that this was the case.[130] Certain studies also excluded participants if they were intolerant or allergic to antibiotics.[94, 95, 99, 100, 122, 123, 132, 134, 135, 137, 141, 152]

The included RCT studies generally described the randomisation process well, performed to reduce selection bias. Randomisation (often random sequence generation was used with computer generated randomisation) was rated as having a high risk of bias in only four out of 18 RCTs (22%, Figure 2-3).[100, 120, 128, 137] For these studies issues that arose include confounding by indication in that randomisation was performed differently for the different arms, for example, no randomisation occurred for the antibiotic arm in the Little *et al.* (2014) study but patients were entered into a non-randomised immediate prescription group if the physician deemed patients definitely requiring antibiotics.[128] In this instance this places selection and performance bias at high risk and introduces confounding by indication (more specifically, confounding by severity, where the indication influences both the use of intervention and is a risk factor for the outcome).[153] In the Bucher *et al*. (2003) study the inclusion criteria were modified twice during the trial and during randomisation.[100]

Although the majority of the studies reported complications this was not their primary objective, and the study designs and sample sizes did not allow consideration of the rare outcomes that are the focus of this review. The older studies published in particular had extremely low sample sizes; Howie et al.

(1985) and Taylor et al. (1983) used estimates for denominators and had exceptionally small sample sizes for the numerators used (both n<40, Table 2-2).[124, 136] Due to the smaller sample size, these studies contained less power and consequently greater uncertainty in the results.

Registers and databases used to track participants are often compulsory to complete and generally robust, and loss to follow-up is often minimal in nationwide registers. However, in a few studies which did not use databases, attrition bias seemed to be evident; for example Crocker *et al.* (2012) reported a low response rate, particularly from controls (60% for cases, 30% for controls).[125] Marchetti *et al.* (2005) reported a response rate of 61% at follow-up visit 30 days after first contact (with 395 cases being excluded from the analysis due to performance bias with incomplete recording of information by the paediatricians).[130] Certain studies reported patients withdrawing from the study prior to assessment of outcomes or cases where medication was discontinued, due either to exacerbation of symptoms or antibiotic-related side effects, or where antibiotics were required to prevent treatment failure.[122, 134]

Figure 2-2 'Risk of bias' and Quality assessment summaries: review authors' judgements about each methodological quality item for each included study

a) Randomised controlled trials "Risk of bias" summary

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Adherence	Blinding of outcome assessment	Outcome measurement technique	Incomplete outcome data	Selective reporting	Other bias
Autret-Leca (2002)	+	+	+	-	?	?	+	?	?
Bucher (2003)	-	+	?	-	+	+	?	+	-
Chapple (1956)	-	-	?	-	-	?	-	?	?
Dagnelie (1996)	?	+	+	+	+	?	+	?	?
De Meyere (1992)	?	+	+	+	+	-	?	?	?
De Sutter (2002)	+	+	+	+	+	?	?	?	?
Howe (1997)	+	+	+	?	?	-	-	-	-
Little (1997)	?	?	-	?	?	-	?	-	+
Little (2014a)	-	-	-	-	?	?	+	?	?
McCormick (2005)	+	?	-	+	-	-	?	-	?
Mygind (1981)	?	+	+	+	?	+	+	-	?
Stalman (1997)	?	+	+	+	+	?	-	?	?
Tahtinen (2011)	+	+	+	+	+	-	?	+	-
van Buchem (1981)	-	?	?	-	?	+	?	?	-
van Buchem (1997)	+	+	+	+	+	+	+	+	-
Zwart (2000)	?	+	+	-	-	-	?	?	?
Zwart (2003)	?	+	+	?	+	?	?	?	?

b) Cohort studies quality assessment summary

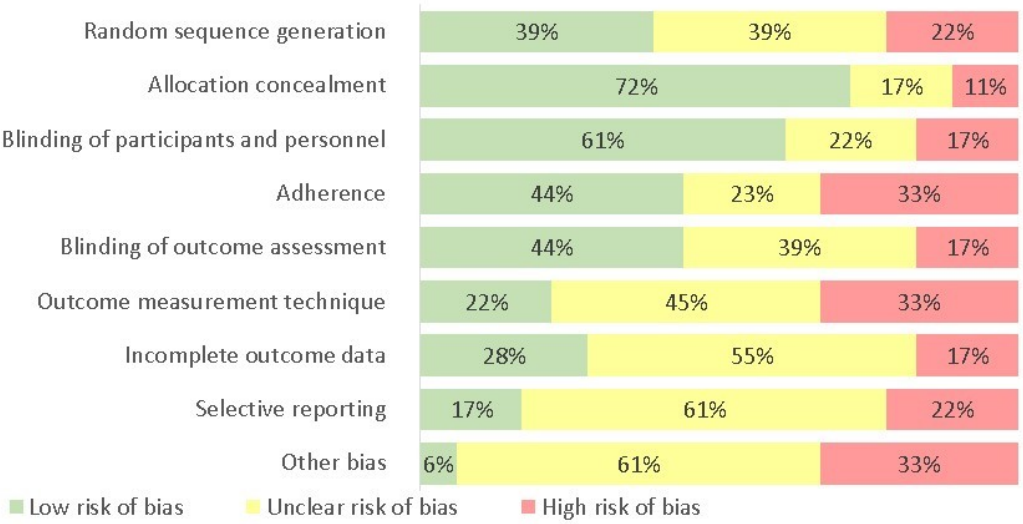
Study	Did the study address a clearly focused issue?	Was the study primary outcome to address the issue of focus in this review?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias? - based on the measurement	Was the outcome accurately measured to minimise bias? - based on blinding of outcome assessment	Have the authors identified all important confounding factors?	Have they taken account of the confounding factors in the design and/or analysis?	Was the follow up of subjects complete enough? Were there differences in the participants lost to follow up?	Was the follow up of subjects long enough/adequate?	Was the outcome data relatively complete? i.e. Attrition and exclusions from the analysis.	There is minimal possibility of selective outcome reporting?	Do you believe the results?	Can the results be applied to the local population?	Do the results of this study fit with other available evidence?
Fry (1958)	+	-	?	-	+	-	-	-	+	+	+	-	-	-	-
Howie (1985)	+	+	?	?	+	-	-	-	?	?	-	-	?	?	+
Little (2014b)	+	+	?	?	?	+	?	+	+	+	+	+	+	+	+
Marchetti (2005)	+	-	+	?	?	?	+	+	?	+	-	+	+	+	+
Meropol (2013)	+	+	+	+	+	?	-	+	?	+	?	?	?	+	+
Petersen (2007)	+	+	+	?	?	?	?	+	?	+	?	?	?	+	+
Taylor (1983)	+	?	?	-	-	-	-	-	-	?	-	?	-	?	+
Thompson (2009)	+	+	?	?	?	?	-	+	+	+	+	?	?	+	+
Winchester (2009)	+	+	+	+	-	?	?	-	+	?	?	-	-	+	+

c) Case-control studies quality assessment summary

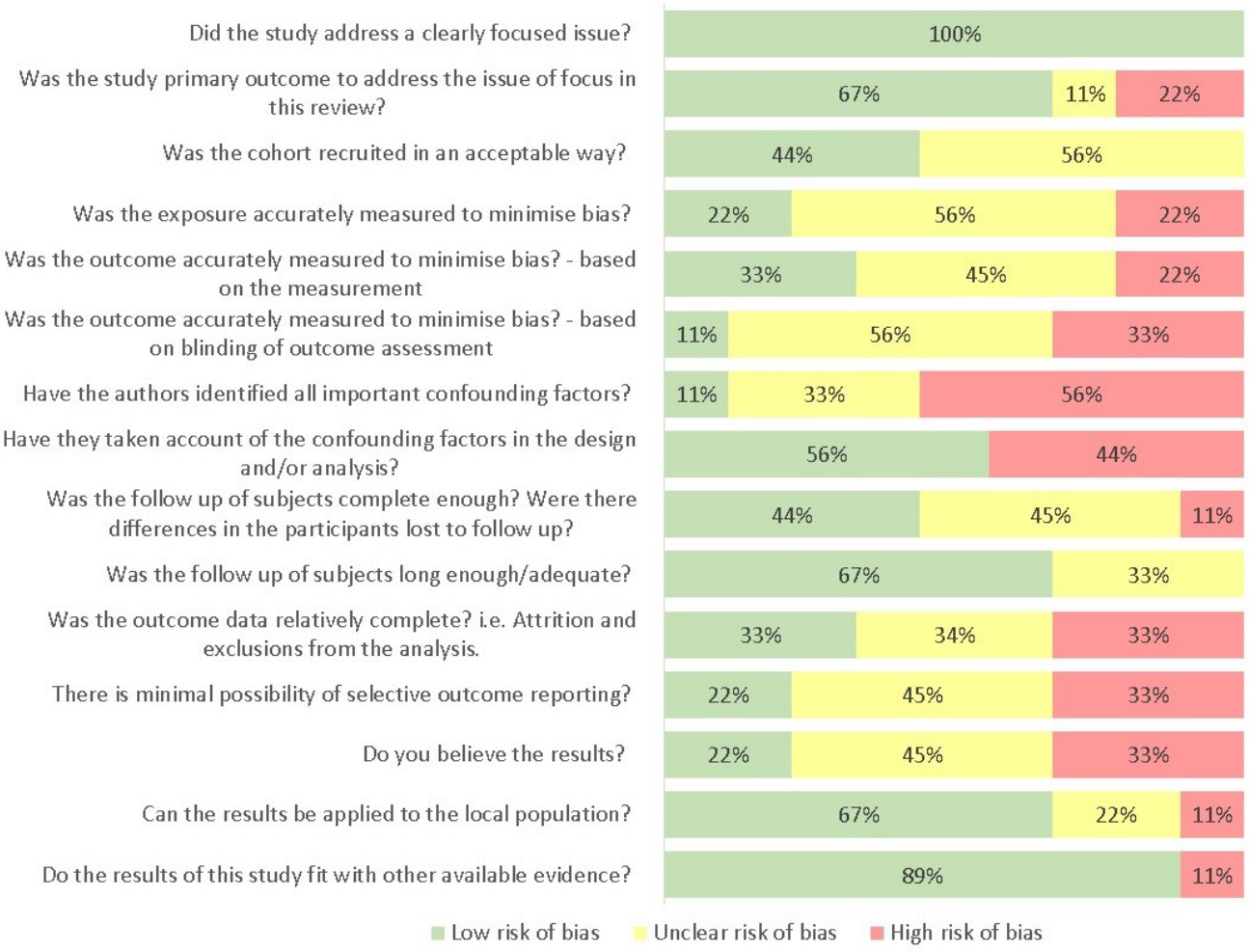
Study	Did the study address a clearly focused issue?	Was the study primary outcome to address the issue of focus in this review?	Did the author use an appropriate method to answer their question?	Were the cases recruited in an acceptable way?	Were the controls selected in an acceptable way?	Was the exposure accurately measured to minimise bias? - based on measurement	Was the exposure accurately measured to minimise bias? - based on blinding of exposure assessment	What confounding factors have the authors accounted for?	Have they taken account of the confounding factors in the design and/or analysis?	How precise are the results? How precise is the estimate of risk?	Do you believe the results?	Can the results be applied to the local population?	Do the results of this study fit with other available evidence?
Crocker (2012)	+	+	+	+	+	+	?	+	+	?	?	?	+
Dunn (2007)	+	+	?	+	+	?	+	+	+	-	?	?	?

Figure 2-3 "Risk of bias" and Quality assessment summaries: Methodological quality presented as percentages across all included studies

a) Randomised controlled trials "Risk of bias" summary



b) Cohort studies quality assessment summary



c) Case-control studies quality assessment summary (2 studies)

2.4.6 Random effect meta-analysis

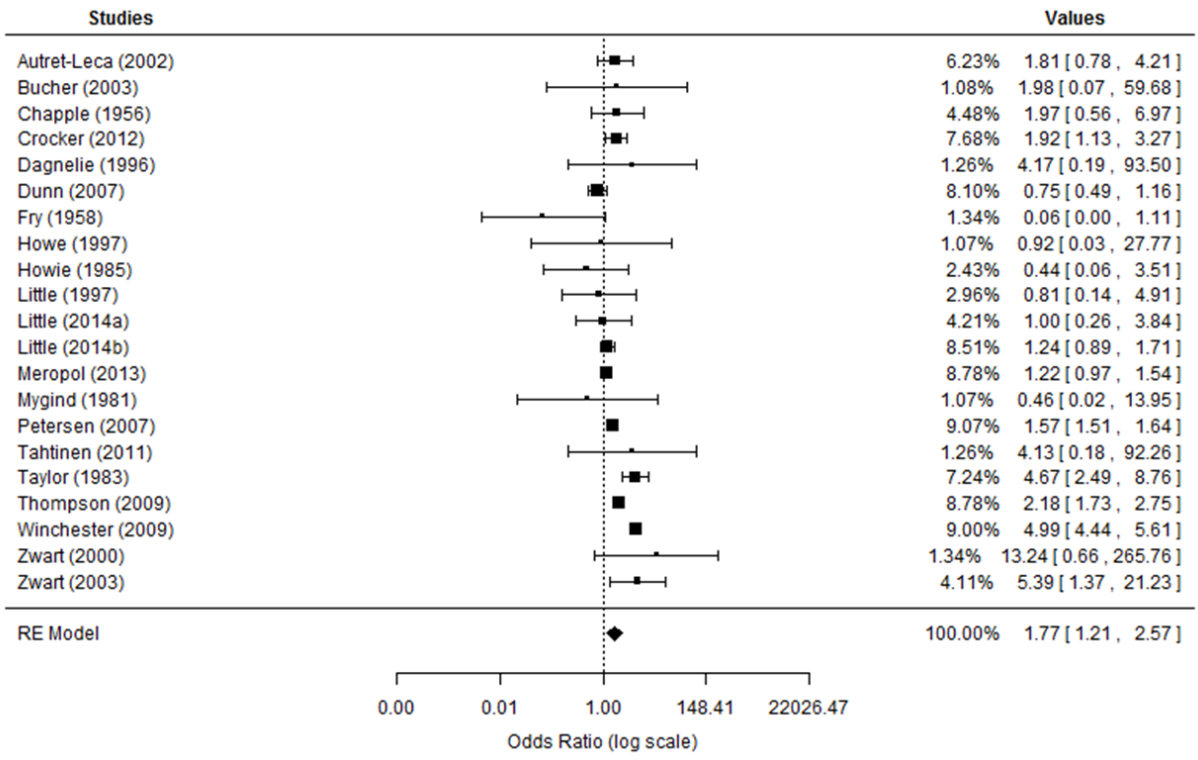
Homogeneity across the studies regarding high-income settings and similarities in inclusion criteria precluded the statistical pooling of results in a meta-analysis. Although there were concerns around differences with older studies and those of different designs (experimental and observational), it was thought that these differences could be attenuated through sensitivity and sub-group analyses.

In instances where no complications were found in either exposed or unexposed groups, the findings were not included in the meta-analysis. This was the case in seven studies.

Figure 2-4 shows a forest plot of the effect estimates from the individual studies and the overall summary estimate. The plot also provides a useful visual summary of the review findings, in that the precision of the individual and overall results are displayed.

The initial meta-analysis (Figure 2-4, Appendix 11) was consistent across the random-effect and fixed-effect analytical methods with slightly wider confidence intervals in the random-effects model, as would be expected (fixed model overall effect: 1.77 [1.71 - 1.84]; random-effects overall effect: 1.77 [1.21 – 2.57]). The OR confidence intervals of the included studies, although extremely variable in size, did overlap, indicating statistical homogeneity. However, the 'heterogeneity chi-squared statistic' (Cochrane's Q test) produced a value of 385.98 ([df: 20] p<0.0001). This statistically significant large value is suggestive of heterogeneity across the studies. This test might be underpowered when the event rates are low as is the case with complications reported. The reported I^2 statistic, which measures the variation in the OR attributable to heterogeneity (due to bias between studies, systemic bias or random chance), further provided evidence of considerable heterogeneity (I^2 = 94.82%). Interpretation of results from the meta-analysis should therefore be taken with caution. Using random-effects models are preferential and sub-analyses to try and distinguish variations and diminish heterogeneity were undertaken.

Figure 2-4. Random effects model output of all included studies (excluding studies which found no complications)



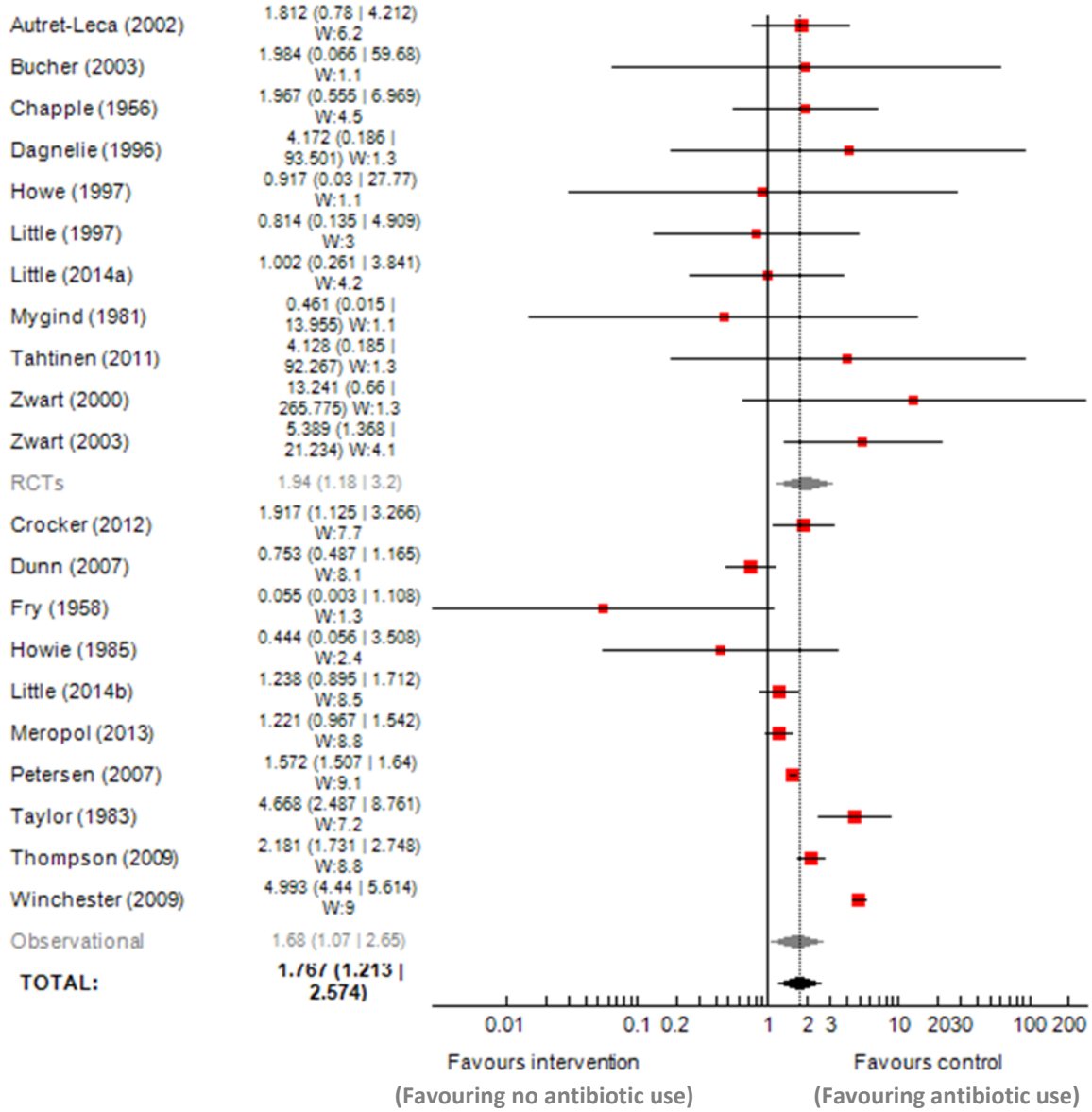
Total events: 4,448 (Intervention [no antibiotics]) 7,110 (Control [antibiotics])
Heterogeneity: Chi^2 = 385.9793, df = 20 (p<0.0001); I^2 (total heterogeneity/total variability) = 94.82%
Test for overall effect Z = 2.9673 (p = 0.0030)

Subgroup analyses

A subgroup analysis was undertaken by study design, dividing studies by experimental or observational design. Figure 2-5 shows that RCTs had a greater pooled OR (1.94, 95% CI: 1.18 -3.2), alongside generally wider confidence intervals compared to the observational studies (pooled OR: 1.68, 95% CI: 1.07-2.65), owing to the smaller sample sizes, which result in greater uncertainty. However, the confidence intervals for the OR of the RCTs overlap, whereas the OR confidence intervals for the observational studies drastically differ in size and do not all overlap. The suggested visual heterogeneity in the observational studies is further supported by the statistical tests, with the Chi-squared statistics (Q test) producing a low value of 6.89 (df=10) for the experimental studies and an exceptionally large 379 (df=9) for the observational studies. The overall Chi-squared value being 386 and the I^2 being 94.8%. When the study designs were separated into two meta-analyses (Appendix 12) the heterogeneity was evidently due to the influence from the observational studies, which are the

study designs known to be more heterogenous in nature. Within the forest plot of the observational studies, the study by Fry *et al.* (1958) seemed to be an outlier, but is one of the older studies reporting data from the 1950s.

Figure 2-5. Random-effects subgroup meta-analysis by study design



Chi-squared test for heterogeneity (df = 20) =	386 (p<0.0001)
I2 (total heterogeneity/total variability) =	94.8%
- Group 1 (RCTs) Q =	6.89 (df = 10)
- Group 2 (Observational) Q =	379 (df = 9)

Analysis including data which assessed infections in children was carried out (Appendix 14). Other age groups, such as the elderly or adults, were not assessed separately, as there were very few to non-existent studies which investigated infections in these age groups alone. The pooled OR increased from 1.77 (CI: 1.21 - 2.57) for overall ages to 2.38 (1.68 - 3.38) for children. The sub-group meta-analysis suggested homogeneity through a small chi-squared test measure of 10.7 (p<0.0001) and an I^2 of 34.6%.

Sensitivity analysis

Older studies were excluded to assess the degree to which these particular studies affected the results. Five studies (2 experimental and 3 observational studies) which were carried out or referred to data pre-1980s were removed from the meta-analysis.[120, 124, 127, 132, 136] The random effects model overall effect increased to 1.81 (1.2-2.73) after removal of the older studies (Appendix 13). Although the chi-squared value slightly reduced from 386 to 369, the I^2 increased from 94.8% to 95.9%. The exclusion of these studies therefore did not improve the reliability of the effect measure.

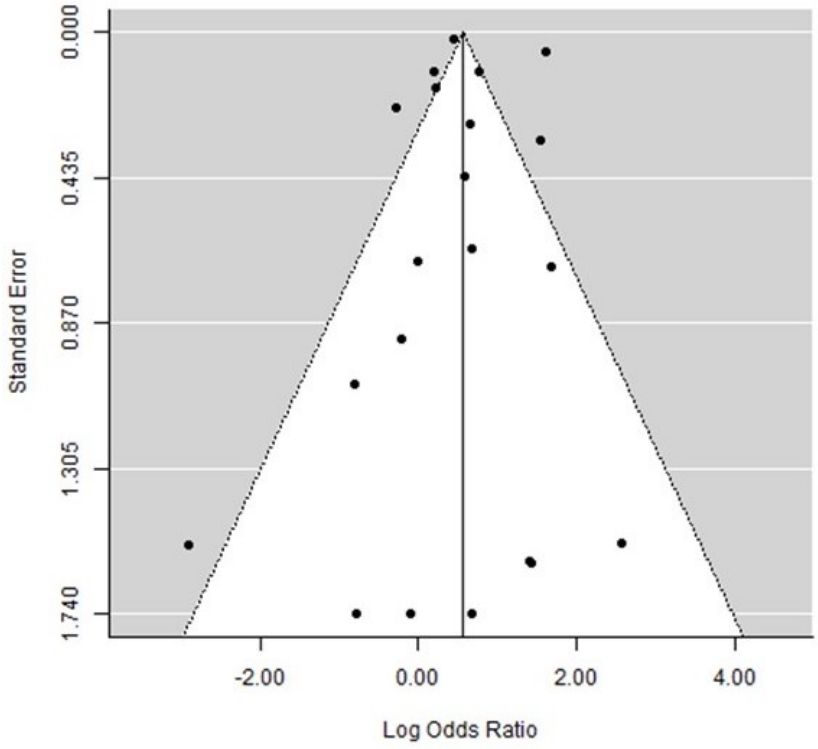
A further sensitivity test was undertaken based on the initial index respiratory infection, to assess whether certain indications were more prone to complications. Of the included studies, where complications were reported and could be included, there were only two clear groups which could be assessed, namely patients who had had an index sore throat or AOM. Studies which reported on these were imputed into meta-analyses (Appendix 15), the pooled OR was 1.8 (1.21 - 2.69) for sore throats and 2.16 (1.76 - 2.63) for AOM, and both meta-analyses had a substantially lower I^2 of 63% and 0.0% respectively.

2.4.7 Publication bias

The funnel plot depicted in Figure 2-6 was used to check for publication bias. The included studies were fairly symmetrical around the pooled OR (shown as a line, 1.77 [CI: 1.21 – 2.57]), indicating no

strong evidence of publication bias. However, the shape of the plot is not a true funnel, with six of the 21 studies (29%) placed outside of the 'funnel' area (the triangle created on an effect estimate and extending 1.96 standard errors either side, representing what would be the inclusion of 95% of studies if no bias exists[119]), which could be related to heterogeneity as previously mentioned.

Figure 2-6. Publication bias funnel plot of included studies



2.4.8 Results of aggregate-level studies and the unintended consequences identified

Twelve studies were included to answer the second objective of this review. A summary of their characteristics and observations can be seen in Figure 2-7. The included studies were too heterogenous in design and intervention type to systematically assess quality.

Not all the studies included in this part of the review assessed a particular intervention. The majority of studies (eight out of twelve, 67%) assessed changing or decreasing trends in antibiotic prescribing and the occurrence of complications, as opposed to an implemented intervention.[51, 139, 143, 144, 147, 148, 150, 151] Of the four studies which focused on the impact of an intervention,[142, 145, 146, 149] two studies

assessed interventions aimed at encouraging "watchful waiting" of antibiotic prescriptions for patients with non-severe AOM and these studies assessed the implemented guidance and potential impact on trends of mastoiditis.[145, 149] Notably one of these studies did not ascertain whether the intervention did indeed impact on antibiotic prescribing, and was in fact noted that the recommendation of "watchful waiting" was not practiced in any of the mastoiditis cases according to the records assessed, which may or may not indicate whether the guidelines were being implemented, as indeed the more serious complicated AOM infections would have been prescribed antibiotics.[145] Similarly, the Palma *et al.* (2015) study, which assessed similar AOM "watchful waiting" guidelines although reporting on mastoiditis trends and antibiotic prescribing, mentioned that the new national guidelines had not seemed to have impacted on prescribing. Hence any changes seen in mastoiditis would be difficult to associate with antibiotic prescribing or the interventions introduced.[149] These two studies both found that there were no statistical significant difference in the impact of the new guidelines on hospital admissions for mastoiditis.[145, 149] Butler *et al.* (2012) assessed the introduction of an educational programme targeted at primary care physicians to improve and reduce antibiotic prescribing, and found a decreased rate of antibiotic dispensing in the intervention group and no subsequent significant impact on the number of hospital admissions for RTIs or related complications (although the intervention group increased by 1.9% [-8.2 - 13.2%] relative to the control group, p=0.72, Figure 2-7).[142] The final study that used an intervention, assessed the introduction of an antibiotic rather than its restriction, which isn't primarily answering the objective of this review, but nonetheless assessed its impact of complications.[146] The results from this study found a relationship between prescribing of ciprofloxacin and reductions in the rate of hospitalisation for asthmatic bronchitis, i.e. prevention of hospital admissions with the increased use of this particular antibiotic. This study assessed the introduction of a particular antibiotic and did not state the trends in antibiotic dispensing as a whole, either in terms of an increase or reduction, or the trends in total antibiotic prescribing prior to the intervention.[146]

Of the studies which assessed variations in antibiotic prescribing trends, only one found that increased antibiotic prescribing was associated with an increase of hospital admissions for RTI conditions and related complications.[143] Another study identified no difference in the incidence of mastoiditis across the study period although there was a significant decrease in antibiotic prescribing for AOM.[139] This study also assessed patient level data (and was included with the individual-level study meta-analyses above) which suggested that prescriptions for AOM significantly reduced the risk of developing mastoiditis within 3 months of an index infection (adjusted OR: 0.56 [95% CI: 0.44 – 0.71]).[139]

The remaining six studies found a protective effect, correlating decreasing antibiotic use with increasing incidence of RTI related complications,[144] or hospital admissions[148, 151] The study by Sharland *et al.* (2005) found no increases in hospital admissions for peritonsillar abscess or rheumatic fever, the only increases seen being for mastoiditis and simple mastoidectomy;[151] increased mortality was noted for pneumonia ($p<0.001$). This study assessed prescribing for lower RTIs which are often more complicated.[150] Two studies suggested a protective effect by noting an increasing trend in antibiotic prescribing and associated statistically significant reductions in admissions for certain outcomes, namely in quinsy and mastoiditis, but not for RTI-related infection overall;[147] and for pneumonia and peritonsillar abscess, but not for mastoiditis, empyema, meningitis, and intracranial abscess.[51]

Figure 2-7. Ecological-level studies included and their characteristics

Study	Study period	Country	Study description	Participants or data	Intervention	Study observations
Butler (2012)[142]	2007 and 2008	Wales, UK	RCT - at practice level	68 general practices (with approximately 480,000 registered patients).	Educational programme (Stemming the Tide of Antibiotic Resistance [STAR]) to reduce antibiotic prescribing in primary care; included practice-based seminar, online educational resources, and practice consulting skills.	Rate of oral antibiotic dispensing decreased by 14.1 per 1,000 registered patients in the intervention group but increased by 12.1 in the control group; 4.2% reduction in total oral antibiotic dispensing (p=0.02). There were no significant differences between intervention and control practices in the number of admissions (30 day episodes) for RTIs or complications to hospital (although intervention group increased by 1.9% [-8.2 - 13.2%] relative to the control group, p=0.72) or re-consultations for RTIs within 7 days of index consultation.
Fernández Urrusuno (2008)[143]	Jan - Dec 2004	Spain	Cross-sectional - GP level	162 GPs (321,034 inhabitants)	Correlating antibiotic use; Using antibiotic prescribing indicators to identify quality of prescriptions.	Higher prescribing of antibiotics was associated with significantly higher number of hospital admissions for RTI (and UTI) complications (p<0.001). Complications include complications of UTI and hospital admissions for these infections as well as complications perhaps arising due to AMR.
Finnbogadottir (2009)[144]	1984 - 2002	Iceland	Time series analysis (ARIMA)	All children with mastoiditis in Iceland diagnosed at the Children's Hospital or ENT department of the University Hospital Reykjavik	Correlating decreasing antibiotic use and incidence of mastoiditis	Incidence of mastoiditis increased significantly during the period (p<0.05) and antibiotic usage decreased significantly in the same period (p<0.05). A correlation was found between decreasing antibiotic usage and increasing incidence of mastoiditis (r= -0.68; p=0.007).
Groth (2011)[145]	1993-2007	Sweden	Pre and post test	All 34 ENT Departments in Sweden treating patients with mastoiditis. Included data for children aged 0-16 years with data spanning 15 years	Data from 7.5 years prior and 7.5 years post introduction of new national guidelines were assessed. Guidelines stated watchful waiting for uncomplicated AOM for patients age 2-16 years.	Subperiosteal/retroauricular abscesses were found in 114 cases (20%) with no statistically significant difference between the periods before and after the introduction of the new guidelines. The total rate of intracranial complications was 2% before and 1% after 2000. The overall complication rate was 25% before and 24% after the new guidelines. Sequelae were extremely rare and only one child developed deafness following meningitis. The disease led to no mortalities during the study period.
Gulliford (2016)[51]	2005 - 2014	England, UK	Cohort with aggregated GP-level analysis	411,226 patients sampled from CPRD which had a registered 4.5 million patients. Rates calculated for each of 610 CPRD general practice included	Correlating antibiotic use and complications following uncomplicated RTI at GP-level. Assessing trends over time and between high and low	RTI consultations prescribed antibiotics declined from 53.9-50.5% in men and 54.5- 51.5% in women. Declining trends in incidence of peritonsillar abscess (1% yearly), mastoiditis (4.6%), and meningitis (5.3%). Pneumonia showed an increase of 0.4% yearly, and empyema and intracranial abscess showed no change over time. General practices in the highest fourth for RTI consultation rate had higher

Study	Study period	Country	Study description	Participants or data	Intervention	Study observations
					prescribing practices (antibiotic prescribers categorised)	incidence rates for pneumonia and mastoiditis. Other complications not associated with the general practice RTI consultation rate. Reducing RTI antibiotic prescriptions by 10% will mean practices issue 2,030 (1134 - 3038) fewer antibiotic prescriptions for RTIs; expected to be associated with 1.1 (0.6 - 1.5) more cases of pneumonia each year and 0.9 (0.5 - 1.3) more cases of peritonsillar abscess each decade.
LeLorier (1998)[146]	Jan 1984 to March 1993	Canada	multivariate time series analysis (ARIMA)	Dispensation data (all causes) obtained from International Medical Statistics. Hospitalisation data (lower RIT ICD-9 codes) obtained from Quebec provincial hospitalisation database.	Introduction of ciprofloxacin to drug listing in Quebec	Antibiotic prescribing of ciprofloxacin assessed (for all causes), but not that other antibiotics were not prescribed. Results indicate that ciprofloxacin dispensed led to an observed hospitalisation rate of asthmatic bronchitis that was 24.6% lower than predicted. A linear dose-response relationship was established between ciprofloxacin dispensation (750mg) and prevention of asthmatic bronchitis hospitalisation for the first 4 fiscal years following the introduction of the drug in Quebec.
Little (2002)[147]	1997–98	England, UK	Combined hospital admissions and prescribing analysis in multiple linear regressions	Hospital admissions for RTIs, RTI complications and RTI related operations. Compared with primary care prescribing of penicillin at health authority level.	Correlating primary care antibiotic (penicillin) use and hospital admissions	Increased penicillin use was associated with a statistically significant reduction in admissions for quinsy and mastoiditis; however significant increase in admissions for tonsillectomy. No significant increase in overall admissions, or for pneumonia or septicaemia.
Majeed (2004)[148]	1996-2002	England, UK	Combined hospital admissions and prescribing analysis in a correlation test (Spearmen's correlation)	One study associated the 23% decrease in overall antibiotic prescribing between 1996 and 2002 with an increase in hospital admissions for respiratory tract infections	Correlating primary care antibiotic (some may not have been for RTIs) use and hospital admissions	Decreasing antibiotic prescriptions (245 to 196 per 1,000 STAR-PU weighted population) was concurrent to significant correlation to increasing standardised admission ratio for RTIs (100 to 115). However, at the primary care Trust level, lower prescribing rates were not associated with higher admission rates.
Palma (2015)[149]	Jan 2007-Dec 2013	Italy	Retrospective analysis of pre and post introduction of new Italian guidelines 2010	Children 0-14 years with signs of AOM and acute mastoiditis presenting at 1 paediatric emergency department.	Italian paediatric guidelines for AOM diagnosis and prevention (2010): prescribe antibiotics where severe, otherwise watchful waiting.	Percentage of antibiotic prescriptions did not vary significantly after introduction of new guidelines. Antibiotics were not prescribed in 43% of cases of acute mastoiditis pre-guidelines, and in 42% post, no statistical difference.

Study	Study period	Country	Study description	Participants or data	Intervention	Study observations
Price (2004)[150]	12-weeks in winter 1993/94 and 1999/2000	England and Wales, UK	Retrospective analysis using negative binomial regression of primary care antibiotic prescribing for LRTIs and pneumonia mortality	Winter antibiotic prescribing data for lower RTIs were extrapolated to population level and presented alongside pneumonia mortality for time periods.	Assessing change over time in mortality for pneumonia and antibiotic prescribing for LRTI. Including sequentially modelling contribution of influenza.	Primary care antibiotic prescribing for LRTIs had declined by 30% whereas excess pneumonia mortality, adjusted for influenza, increased by 50.6%. Reduction in antibiotic prescribing for LRTI was significantly associated with pneumonia mortality ($p<0.001$).
Sharland (2005)[151]	1993–2002	England, UK	Visual time trend analysis of national general practice prescribing data and hospital admissions	Hospital admissions for children 15 years and younger with quinsy, rheumatic fever, or mastoiditis. Prescribing data on drugs issued used.	time trend of decreasing antibiotic use and hospital admissions	Use of antibiotics for children approximately decreased by half across study period (with 34% decline occurring before 1999). No increase in hospital admissions for peritonsillar abscess or rheumatic fever seen, whereas an increase in mastoiditis and simple mastoidectomy was shown (increased by 19%, with sharpest increasing coinciding with sharpest decrease in antibiotic prescribing).
Thompson (2009)[139]*	1990-2006	England, UK	Retrospective cohort	Children (3 months to 15 years) with otitis media. Data from GPRD	to identify risk of mastoiditis within 3 months protective effect of antibiotics.	Mastoiditis incidence remained stable across study period (average incidence: 0.12 [95% CI: 0.11-0.13] diagnoses per 1000 child-years). Antibiotic prescribing significantly decreased for otitis media declined by 49.6%; from 77% in 1990 to 58% in 2006 ($P<0.01$).

2.5 Discussion

This review highlights the current lack of evidence and evaluation of the risk of progression of RTIs into more severe complications when antibiotics are withheld at an index primary care consultation or where there is a population-level reduction in antibiotic prescribing. Studies suitable for inclusion in the systematic review were not very common, with less than half of those included in this review directly addressing adverse effects and complications of infection as an outcome.

2.5.1 Summary of main findings

Half of the 28 studies included in the review revealed that patients may have a greater probability of developing complications where antibiotics are not prescribed immediately compared to patients who are prescribed antibiotics for uncomplicated RTIs (with OR ranging from 1.22 to 5.39, and an anomalous 13.22). Notably a quarter of the included studies reported no complications whether prescribed antibiotics or not and that antibiotics in these instances conferred no benefit. Contrary to the above, six studies (21%) found that complications were more probable in patients who had been prescribed an antibiotic (with OR ranging between 0.06 to 0.92). However, a probable confounding factor in these studies was the fact that patients with more severe infections at initial presentation, who were clinically at greater risk of developing complications, were frequently allocated to the immediate antibiotic prescription group, in this way introducing a potential selection bias. Nonetheless, a key finding throughout was that these events were rare, regardless of whether patients were prescribed antibiotics or not.

Symptom duration and resolution, where assessed, seemed to be slightly shortened and reduced with antibiotic use. Other findings were that gastrointestinal symptoms were often described as side effects of antibiotic prescribing and that patients prescribed antibiotics were more likely than those who were not, to re-consult or relapse. This could also be due to patients who were prescribed antibiotics having more severe infections, making them more likely to require further care. The literature suggests this

could also reflect "medicalisation" of symptoms, where patients associate similar symptoms or conditions with the need to receive antibiotics or medical advice.[141] The literature also suggests that the exposure to certain antibiotics, or the dose or duration of the antibiotic, may not have sufficiently eradicated the pathogen but rather reduced the natural immune response, which could place the patient at an increased risk of reoccurrence of infection and symptoms.[141]

The meta-analysis (which included 21 studies) suggested that the odds of a complication for patients not being prescribed antibiotics is 1.77 times greater than for patients who were prescribed antibiotics (p<0.005). This provides evidence that antibiotics have a small protective effect against development of a severe complication following an index RTI. However, several studies within the meta-analysis had wide confidence intervals (15/21 studies had confidence intervals which crossed the line of null effect), which are reflective of the small-scale studies included in the review, which may not have been powered to a degree large enough to adequately detect rare outcomes.

The patient-level studies included were homogenous with respect to indication (RTI), setting (primary care), and intervention (primary care antibiotic prescribing). However, there was heterogeneity with respect to outcome variables, severity of indication, primary aims of the studies, baseline prescribing, geographic location, demographics/inclusion criteria such as age, and study designs. The sub-group analysis divided studies by experimental or observational designs which revealed very little heterogeneity in the experimental studies (I^2= 0.00%), although heterogeneity was noted in the observational studies. Heterogeneity was further accounted for via random-effects models. However, the tests for heterogeneity and the funnel plot suggest that confidence in the results may be lowered. Notably the experimental studies had a higher pooled OR favouring the use of antibiotics compared to the observational studies, with the difference potentially due to patients in experimental studies being more likely to adhere to drug protocols than those receiving treatment in routine practice. In applying these results there are a number of matters to consider, including the relevance of studies carried out decades ago. It can be argued that older studies may not be relevant to contemporary

practice, in that the course of illnesses and disease has changed, the severity and prevalence of both uncomplicated RTIs and related complications and the clinical criteria defining these illnesses has also altered. These studies were also very small in size and the selection of participants biased. It would therefore be difficult to extrapolate conclusions from these study populations to form the basis for present antibiotic treatment.

Sensitivity analysis for RTIs in children revealed that children not prescribed antibiotics had a higher odds of developing a complication compared to children who were not given antibiotics (OR: 2.4 [95% CI: 1.68 – 3.38]). This could be due to the influence of an effect modifier or cofounding in these results in that the immunological immaturity of young children renders them more susceptible to infections, as well as unintended complications, and AOM is essentially a condition in young children.[135]

The ecological-level studies, which utilised aggregated data, provided contradictory results on the association between antibiotic prescribing and the occurrence of, or hospital admissions for, RTI complications. The majority of the studies primarily assessed changes in the trend of antibiotic prescribing, with only four of the twelve studies assessing interventions. There were uncertainties around the successfulness in reducing antibiotic use in two of these four intervention studies, which subsequently found no statistical significant difference on the impact of intervention on intracranial complications and mastoiditis.[145, 149]

Lower rates of antibiotic prescribing were shown to have no statistically significant impact on hospital admissions for RTIs or complications in two studies[142, 147] (with others reporting no significant changes in the incidence of mastoiditis,[51, 139] empyema,[51] meningitis,[51] intracranial abscess,[51] peritonsillar abscess,[151] rheumatic fever,[151] pneumonia[147] or speticaemia[147]). In contrast, other studies noted a protective effect with antibiotic treatment,[148] specifically a decreased risk of mastoiditis[51, 144, 147] (and simple mastoidectomy[51]), peritonsillar abscess (/quinsy),[51, 147] asthmatic bronchitis,[146] pneumonia,[51] and pneumonia mortality.[150] One study suggested that use of antibiotics was related to an increase in

hospital admissions for RTIs and related complications, however this was likely to also include complications arising due to AMR.[143]

2.5.2 Quality of the review and limitations

The systematic technique used to perform this review was rigorous and provides the first structured method used to assess the risk of complications where antibiotics were not prescribed, or where there was a reduction in antibiotic prescribing for uncomplicated RTIs at a population level. Whilst the strengths of a systematic review and pooling of evidence in meta-analyses are well described, the included studies inherently have certain limitations that should be mentioned when extrapolating from the findings.

Different study designs were included within the literature review in order to overcome selection bias via recruitment and overcome issues with small sample sizes. Despite randomisation, selection bias may be introduced in trial designs, whereas observational studies tend to include participants who are more representative of those seen in routine primary care. This was the case with the included experimental studies, as participants were often recruited following a primary care consultation using similar inclusion criteria's as the observational studies. However, as with the experimental designs the interventions received by individuals was decided by random allocation (with 89% rated as low or unclear risk of bias for allocation concealment), which differs from observational studies which were determined by common practice and representative of "real-world" choices. Participant performance would also often vary in trials compared to observational settings, in that participants were more likely to adhere to the full and correct course (dose and duration) of antibiotics. Hence the effect of antibiotic prescribing in routine practice may be smaller than the evidence suggested by the included experimental studies and respective pooled estimate, although there was an overall 56% of included trials rated as having a high or unclear risk of bias for drug compliance and adherence. Findings from the observational studies are prone to confounding by indication, which arises when individuals are

prescribed antibiotics, as they are inherently different to those not given the antibiotics (i.e. patients with more severe infections have an “indication” for the use of antibiotics and would be treated). As patients with these severe infections are more likely to develop complications, this would tend to give an underestimation of the protective effects of antibiotics within the observational studies.

Eighty-nine percent of included cohort studies had high or unclear risk of bias for not fully identifying important confounders. These biases may have influenced the higher pooled estimate, which favours the use of antibiotics, seen in the trials compared to observational studies. The RCTs generally had insufficient power to examine the effect of antibiotic treatment on the occurrence of rare outcomes and is limited in external validity due to this. Each design had its drawbacks, however, use of observational studies complements the data from trials and suggests a possible true effect may lie between the two grouped results as provided by the overall pooled estimate, which increases the generalisability of the findings.

Within the review, a minority of studies focused on assessing the development of an uncomplicated infection into a more severe infection as a consequence of not receiving timely antibiotic treatment. Of the studies which met the inclusion criteria for this review, only ten (36%) focussed on assessing this as a primary outcome. Several studies incorporated data for complications but had not tailored the design or sample size sufficiently to answer the question posed by this review. The wide confidence intervals (predominantly seen with smaller experimental studies) in the forest plot suggests the study results were not very precise or powered adequately to assess these rare outcomes. Furthermore, it is likely that studies constructed to identify complications as the primary aim would report a higher frequency than studies which were not specifically targeting these outcomes. This is not necessarily due to experimenter or reporting bias (albeit these studies were prone to selective reporting of complications as they were of primary interest and sought after outcomes) but perhaps due to limited follow-up time or infrequent monitoring to reliably detect complications which may arise in studies not tailored on this outcome. Furthermore, certain studies not assessing complications as the primary

aim amended treatment during the study which would have subsequently impacted on the effects seen. For example, Bucher *et al.* (2003) following a patient experiencing a brain abscess altered the inclusion criteria to prevent further complications (with all patients with a C-reactive protein level greater than 100mg/L being excluded thereafter),[100] while Zwart *et al.* (2003) excluded participants during the study due to imminent quinsy (n=28) and suspected scarlet fever (n=9).[141] These studies which excluded participants with severe infections or those who would have been at a higher risk of complications would have shifted any effects towards the null and underestimated the effects seen in studies not primarily assessing the rare complications of this review.

As heterogeneity was found, a random-effects model and sub-group and sensitivity analyses were undertaken to compensate for this. Remaining heterogeneity may be due to clinical heterogeneity among the included studies with different levels of severities of infection, or the propensity of different RTIs to increase in severity. A sub-analysis was undertaken to investigate whether certain groups of RTIs would benefit more so from the use of antibiotics in preventing complications. However, very few studies assessed the same group of infections, consequently this was only completed for sore throats and AOM. Besides the diagnostic groups, antibiotic duration, dosage and antibiotic used varied to some extent. This is not considered to have impacted on the results seen as current evidence indicates a very small absolute treatment difference of 3% in treatment failure at one month following seven-day antibiotic use versus longer treatment regiments.[106]

A degree of publication bias may have existed, which may be related to difficulty in the search strategy in attempting to identify complications. Most of the excluded studies referenced unintended consequences as outcomes following the use of antibiotics rather than where they were withheld, that is, the emergence of resistance, selection of pathogenic organisms, toxicity, and antibiotic side effects such as gastrointestinal infections or symptoms. To minimise publication bias, multiple databases were searched, including the grey literature and references, and there was no limit on language. Although studies were not limited with regards to where they were performed, all the studies were conducted

in high income OECD countries (Organisation for Economic Co-operation and Development), predominantly the UK and the Netherlands. This could imply that primary care data are more readily accessible to researchers in these countries, or it could be suggestive of publication bias, or bias in the search strategy and identifying studies with terminologies specific to European countries, although one study identified was undertaken in the USA. Hence while this review may be representative of the UK populations, it would limit generalisability to other countries or countries with different health care system structures or clinical settings.

The inclusion of aggregate studies as a sub-analyses of this review complements individual-level study findings and would be pertinent to inform policy. A limitation of the findings from the aggregate-level studies was that the study designs, methods and populations were extremely heterogenous. Studies based on data from populations are also open to ecological fallacy, which notes that exposure and outcome in any one individual may not be linked. However, these studies were well powered to provide useful data on correlations.

Since the time of which the systematic literature review was undertaken, subsequent relevant literature has been published. Indeed, a study by Balinskaite *et al.,* would have been eligible for inclusion within the ecological studies. Findings from this research include no statistically significant correlation between a national AMS scheme (the QP) and complications.[91] Cushen *et al.* would also have been eligible for inclusion within the patient-level studies. Findings from this paper suggest that antibiotic prescriptions for AOM were associated with reduced odds of developing mastoiditis, and for acute sinusitis leading to brain abscess; with serious complications rarely occurring (with large Numbers Needed to Treat).[154]

2.5.3 Findings in relation to other published evidence

Systematic reviews of RTIs often focused on their treatment, rather than complications that may arise where antibiotics were not prescribed,[13, 52, 104-107, 155-158] although some included studies which suggested complications of RTIs were reduced when antibiotics were prescribed immediately,[52, 104] or mentioned no significant difference between cases or rates of complications.[13, 105-107] Smith *et al* (2017) mentioned a study which found reduced complications with antibiotic use to be particularly evident in elderly patients.[104, 133] Spinks *et al.* (2013) also found that antibiotics reduced the incidence of AOM, acute sinusitis, and quinsy, rheumatic fever, and potentially acute glomerulonephritis although there were very few studies within the review which reported on glomerulonephritis; this along with other outcomes, was the case in this review, with wide estimate confidence intervals making it difficult to infer that antibiotics protect sore throat sufferers from these outcomes.[52]

Five systematic reviews directly assessed the value of antibiotics in preventing infectious or disease complications for certain RTI indications.[103, 159-162] Of these, four found no statistical evidence of protective effect of antibiotics on the occurrence of complications.[103, 159, 160, 162] Specifically, Alves Galvao *et al.* (2016) found no statistical evidence of a protective effect of antibiotics following an acute RTI in children on the occurrence of otitis media or pneumonia and no reported cases of mastoiditis, quinsy, abscess or meningitis.[159] Gadomski *et al.* (1993) also assessed evidence of antibiotic treatment for children with upper RTIs and found no association with the prevention of pneumonia.[162] Falagas *et al.* (2008) found no difference in disease complications for acute sinusitis.[103] Vouloumanou *et al.* (2009) found that although severe complications of AOM, such as mastoiditis and meningitis, were still being reported at low rates in the community, they were rarely observed in the findings of the review.[160] The last meta-analysis and systematic review assessing complications, suggested that antibiotic treatment does protect patients with sore throat against acute rheumatic fever, but not against acute glomerulonephritis.[161]

Although the above findings contradict somewhat the findings from this review, particularly for children and the potential positive impact antibiotics may have on reducing subsequent more severe infections, the comparison of findings highlights the lack of strength and power in the majority of studies and the extremely low numbers of outcomes used to impute into the meta-analysis. Hence, the review emphasises the lack of robust evidence, at both patient- and aggregate-level, assessing the influence of antibiotic use on the propagation of bacterial infections and whether the odds of these more severe rare infections occurring are of clinical significance.

2.6 Conclusion

Whilst the review found an association at patient-level of an increase in odds of a complication where antibiotics were withheld, and the aggregate data suggest that certain conditions or age-groups may benefit from antibiotic use, there were many inconsistencies and questionable precision in the findings. The aggregate data were too heterogenous for valid comparisons and the patient-level studies included homogenous experimental studies, although these were often small in scale. The observational studies, which suggest heterogeneity, were vulnerable to various biases, particularly bias by indication, and the lack of ability to confidently compare the groups assessed. Hence, although antibiotics were related to a small reduction in the odds of patients developing a more severe infection compared with placebo, the evidence was insufficient for definitive recommendations. In high-income OECD countries most cases of uncomplicated RTIs resolve without complications, and occurrence of complications were rare. Benefits must therefore be weighed against the possible harms of prescribing antibiotics, specifically the development and spread of AMR. The literature suggests that antibiotics may be most useful for children and that an observational approach of “watchful waiting”, as national guidance suggests for several RTI indications, would be justified.

2.6.1 Implications for practice

Further high-quality evidence is needed before pragmatic recommendations can be made. However, this may prove difficult due to ethical implications of decreasing access to antibiotics where it may be required. Further quasi-experimental designs may be beneficial, particularly research looking at decreases in antibiotic use at the population level, as would be shown following the introduction of the Quality Premium in England. This approach might identify whether a threshold in antibiotic reduction has been reached, or whether there are limited effects on unintended consequences.

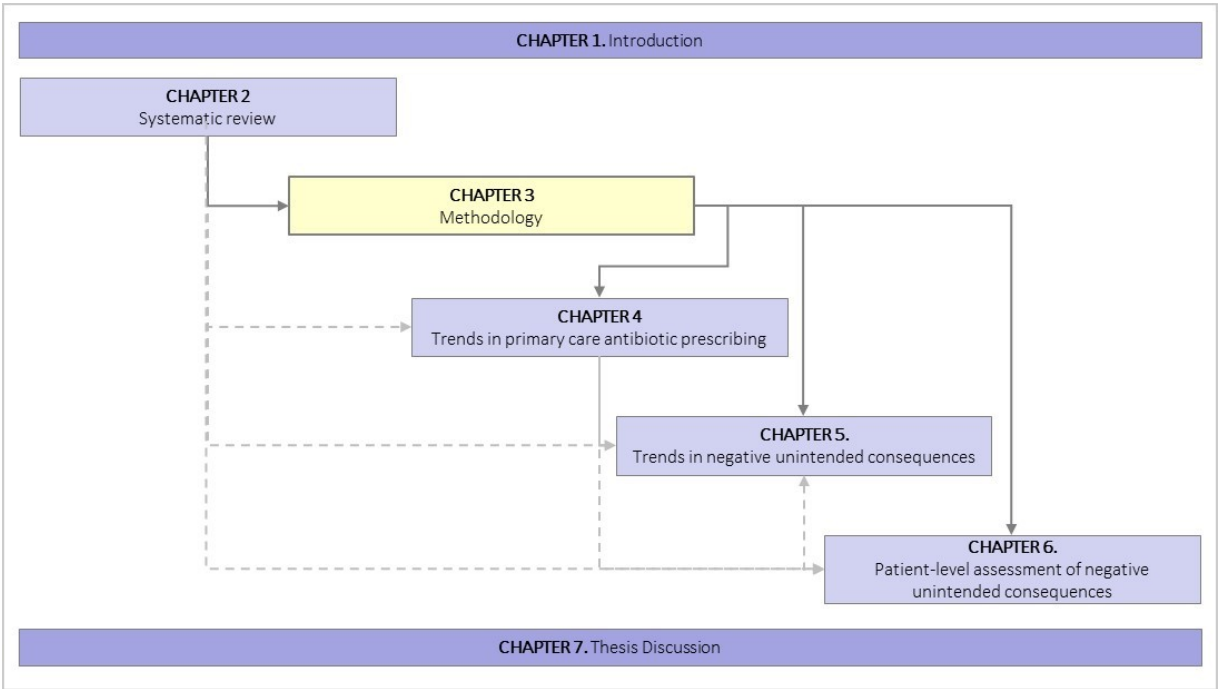
2.6.2 Implications for research

The studies in this systematic review and respective findings provided evidence and guidance as to the complications and diagnoses groups which should be focused on in Chapters 5 and 6 (which assess the unintended consequences of the QP), and will be utilised in Chapter 3 (Methodology) to inform a Delphi method to identify infectious pathways.

The effect of antibiotics on RTIs may be complex and dependent on timing of use in relation to clinical course of infection. Further research with distinction of clinical severity or research which permits sub-group analysis of more RTI groups would be beneficial as certain infections may be more prone to increase in severity and progress into secondary infections. Assessment by different age groups and more research as to the impact on decreasing antibiotic use in the elderly (as well as children) would be useful to provide more conclusive recommendations, as has been assessed for UTIs.[163]

Many of the patient-level studies were potentially underpowered to detect small but clinically significant effects on the incidence of complications. Given the high incidence of RTIs, even a small relative change might translate into a large public health effect. Aggregate-studies could provide information on the effect on populations. Further research using quasi-experimental research would be beneficial as these would be well powered and generalisable. Furthermore, to strengthen quasi-experiments, linking patients' acute RTI indications to subsequent complications would be valuable.

CHAPTER 3



Summary:

This chapter discusses in detail the methodology used to identify infection pathways; the initial uncomplicated RTIs consulted for and subsequent severe infections which may develop where antibiotic treatment is not provided (informed by Chapter 2). This chapter also outlines the methodologies used throughout the remainder of the thesis, from: the data sources used, the process of data management, data linkage of national data sources, and modelling the QP impact using interrupted time series analysis (used in Chapters 4 and 5) and hierarchical multivariable analysis (used in chapter 6).

3 METHODOLOGY

This chapter aims to review the methods used to test the thesis hypotheses, namely whether the intervention of interest, the Quality Premium (QP), had the intended impact of reducing antibiotic prescribing in primary care and whether there were any unintended impacts across healthcare settings. It describes the data sources used and how they were obtained and linked, the identification of the study cohort, and the statistical methods used.

3.1 Data sources

A number of routine databases which continuously collect defined data using standardised definitions for covariates from a real-world setting were used. They included the Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data. Linkage of the datasets can depict the interactions throughout a patient's healthcare pathway (primary care, secondary care and outcome in terms of mortality), and identify the occurrence and severity of subsequent infections.

3.1.1 Clinical Practice Research Datalink

CPRD, formerly known as the General Practice Research datalink (GPRD), is a primary care database containing patient-level anonymised longitudinal medical records dating back to 1987, from 674 general practices across the UK (England, Scotland, Wales and Northern Ireland), covering 6.9% (approximately 11.3 million) of the national patient populations.[164, 165] This sample is largely representative of the national UK population with regards to age, sex, ethnicity, consultation and prescribing levels.[164, 166] The CPRD data are collected as part of routine clinical practice in primary care by general practices using the Vision Clinical System® software, a widely used GP software system, to maintain patient electronic health records. Pseudo-anonymised patient information is automatically

extracted from the Vision Clinical System and uploaded to the CPRD database. This is updated after quality checks are completed in a monthly build and made available for researchers to use on the online CPRD-GOLD server.[164] Practices voluntarily participate in the contribution of the data collected, with patients within a participating practice, being able to opt-out of data sharing of their personal records. Once collected, the extracted CPRD database contains detailed information on patient diagnoses, symptoms, lifestyle, prescriptions, laboratory and diagnostic tests, immunisations, hospital referrals, as well as patient-level and general practice-level demographic information.[165]

Data are recorded at patient level using the Read clinical coding system. This is a hierarchical clinical coding system developed in the 1980s, superseding the previous Oxford Medical Information System (OXMIS). There are approximately 100,000 alphanumeric Read codes which are dedicated to primary care coding and form a dictionary which is extensively used in the UK to record clinical events, patient diagnoses, symptoms and process of care during a patient consultation.[167] These standardised codes are regularly audited to ensure quality reporting.[165]

Prescribing information (of drugs and appliances) is recorded within CPRD using the Gemscript product code system. These codes can either be identified by their product or drug substance name or by mapping to the classification chapters and codes used by the British National Formulary (BNF).[167, 168] The 15 BNF chapters and related codes are widely used in the UK for information and to aid clinical decisions of prescribers, pharmacists and other healthcare professionals, providing key information and advice on selection, prescribing, dispensing and administration of medicines covered in the UK. The prescribing information used in this research was extracted using the BNF mappings.

3.1.2 Hospital Episode Statistics

The HES database is an administrative record-based system managed by NHS Digital (http://content.digital.nhs.uk/hes), formerly known as the Health and Social Care Information Centre

(HSIC), and provides a data warehouse of all English National Health Service (NHS)-related health care provider activity, which includes details of all admitted patient care, outpatient appointment attendance, and Accident and Emergency (A&E) attendance. Data are extracted from a data warehouse on a monthly basis, and an annual refresh is completed at the end of the financial year to correct any known data quality issues.

The HES Admitted Patient Care (APC) data contain details for every NHS hospital admission in England. The patient records include private care patients and residents outside of England who were treated by an NHS health care provider. The HES extract utilised in this research used the release of the HES APC data linked to CPRD GOLD (set 15) which covered the study period April 1997-July 2017; this included the study period required (April 2010, later amended to April 2011, to March 2017).

The data from HES include clinical information on the primary diagnosis (codes for diseases, signs and symptoms, and causes of injury or diseases) when a patient is admitted, together with any other diagnosis codes which a patient had recorded during their hospital stay. The diseases, health conditions and events during a hospital stay are categorised based on the International Classification of Disease 10th revision (ICD-10) codes. ICD-10, which comprises 22 chapters, is a diagnostic tool used to uniformly classify diseases, procedures and health conditions for the purpose of recording on health records or coding cause of death.[169]

3.1.3 Office for National Statistics mortality data

There is a legal requirement to certify and register all deaths which occur in England and Wales. All such registered death certificates are collated and form a mortality data repository maintained by the ONS, which provides the most complete data source for mortality statistics. Cause of death is obtained from the Medical Certificate of Cause of Death (MCCD), which is completed by a medical practitioner when the death is certified, with information coded using ICD-10. Regular quality checks and

validations are completed by ONS to ensure there are no inconsistencies and to ensure completeness in receiving all death registrations.

The ONS extract utilised in this research used the ONS to CPRD GOLD linkage (set 15), which covered the period from 2nd January 1998 to 19th September 2017; this included the study duration required. In January 2011, the software used to code the cause of death was updated from ICD-10 v2001.2 to ICD-10 v2010; changes included in this update may have affected ascertainment of the causal sequence and may make consistency pre- and post-January 2011 problematic. Thus, assessment of hospital admissions (HES), and mortality trends (ONS) were considered from April 2011 to March 2017.

3.1.4 Ethical approval and data access

No patient-identifiable data were used and no new information was collected for this research. Approval to use the CPRD database, and link this data to other data sources, was acquired from the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research. ISAC approval was obtained on the 30 November 2016, (protocol number: 16_129R; Appendix 16 and Appendix 17).

3.2 Patient representative participation in the research

Two patient representatives reviewed the plain English summary of the ISAC CPRD protocol and helped to maintain a good understanding of the patients' perspective throughout.

3.3 Appropriate classifications and code lists

A range of approaches were used to identify the appropriate classifications and subsequent codes of antibiotics, the initial RTI infection consulted for in primary care and the subsequent more severe infections assessed. These are outlined below.

3.3.1 Defining antibiotics and general practice antibiotic prescribing

The cohort of patients from CPRD were analysed to see whether their consultations included antibiotic prescriptions. To do this, a prescription was linked to a patient's consultation if both occurred on the same day. The antibiotic therapy codes were identified and categorised using the BNF sub-chapter 5.1.[168] The analysis was restricted to systemic antibiotics by excluding anti-tuberculosis (BNF chapter 5.1.9) and anti-leprotic (BNF chapter 5.1.10) drugs; which are not prescribed for uncomplicated RTIs. Their exclusion is in line with the published literature and common practice when assessing antibiotic trends.[33, 47, 170]

The BNF sub-chapters were used to categorise broad-spectrum antibiotics and included broad-spectrum penicillin's (including co-amoxiclav), cephalosporins and quinolones. The CPRD code-browser was utilised to translate the relevant BNF codes into CPRD product codes, which were then used to identify whether a patient had been prescribed an antibiotic, and whether the antibiotic was broad-spectrum.

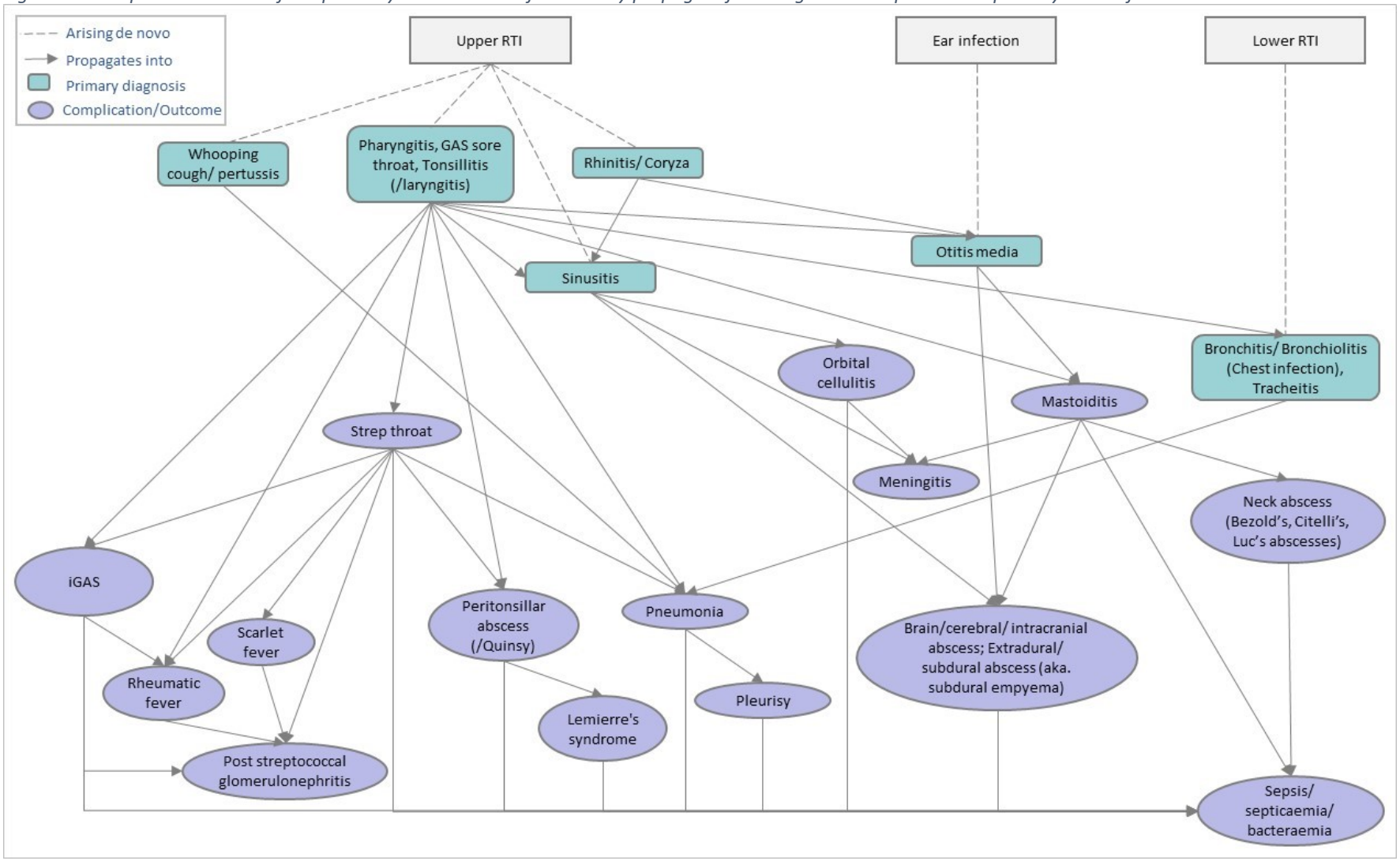
3.3.2 Defining infectious pathways, index infections and outcomes – Modified Delphi method

A three step modified Delphi approach was used to identify respiratory indications a patients may initially consult with, what these infections may progress into, and further down the infection pathway, what the more severe complications may be (i.e. when a bacterial infection has not been treated with

antibiotics and has developed into a more serious complication). The Delphi method is a rapid, interactive way of gaining opinions from independent experts. This multi-stage approach provides a robust and transparent method of exploring the knowledge and expertise of a group of people who have been defined as having specialist knowledge on a particular subject, and obtaining a consensus over rounds of investigation.[171] A modified method was used which combined the expertise of several individuals and the published literature. The method is relatively rapid, more so than organising a focus group, as the participants did not need to be in the same vicinity to reach agreement, and individuals were also able to express their own opinions as opposed to "group thinking" whilst still reaching an overall agreed and informed judgement.

The initial stage included reviewing the literature to establish the likely infections for exploration. The index infections and complications identified in the systematic literature review (Chapter 2) were used to draw initial pathways of infection, identifying the primary indication a patient would consult with and subsequent complications, which are biologically plausible and where patients may be at an increased risk if antibiotics are withheld or delayed. This provided the content to be assessed by the Delphi panellists. Five experts who were approached all agreed to participate. All five had clinical expertise and had a breadth of knowledge around AMS, AMR, infections in children, and infections in primary and secondary care. Amendments were made to the preliminary infection pathways based on the feedback provided and the Delphi process was applied over another round of consultation. Three such rounds were implemented, until the iterative process converged towards a consensus of opinion and a point of diminishing returns had been achieved. The experts were informed of the agreed list of infection pathways, at which point no further amendments were suggested or differing opinions made. The finalised infection pathway, classifications of indications and the outcomes defined through this iterative process, can be seen in Figure 3-1.

Figure 3-1. Graphic illustration of the pathways in which an infection may propagate following an uncomplicated respiratory tract infection



-All primary diagnoses can potentially lead directly to sepsis. In order to simplify the diagram arrows from complications/outcomes leading to sepsis have been included, but not the primary indications.

- Certain conditions commonly present as the first indication to GPs, without previous consultations (e.g. Mastoiditis with no prior consultation for acute otitis media), i.e. these conditions may present as a primary infection as well as a complication. However, often guidelines for these more complicated infections are to prescribe antibiotics, hence have been included as outcomes only.

3.3.3 Selection and grouping of appropriate READ codes

The following strategy was implemented to develop lists of medical (READ) codes for the primary uncomplicated infections and the complications of interest (Figure 3-1).

A rapid literature search was completed using PubMed, the CPRD bibliography (https://www.cprd.com/Bibliography), and the Clinical Codes repository website (https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/articles/) to identify previous studies which had utilised and published supplementary CPRD Read codes related to the index conditions and outcomes. These references were used to compile diagnostic reference tables of text strings and codes, which included disease classification codes along with codes for symptoms and clinical signs, for both the index RTI infection categories[46, 77, 133, 140, 147, 151, 172-176] and the related complications.[133, 147, 151, 177]

The diagnoses and descriptions identified for each condition were used to develop lists of text strings to enable searches to be undertaken (e.g. BSI, *blood*inf*, *sepsis*). These were searched (using text string wildcard for the keywords and synonyms, and code stem searches) in the most current CPRD Read code dictionary. This updated any historic terms and codes found in the literature (particularly for GPRD codes), and included any additional codes and terms which may have been missed or had been recently introduced and were relevant for inclusion.

The resulting CPRD Read codes were discussed and reviewed by a practicing GP, (Appendix 18 and Appendix 19). The lists of index primary conditions assembled included symptoms and diagnoses which would normally be prescribed or not prescribed antibiotics; e.g. conditions relating to a bacterial/streptococcal upper RTI (where an antibiotic prescriptions may be appropriate) as well as viral related RTIs (where antibiotics would not be appropriate) were included, as complications could develop from those missed index infections in the first instance and coding or misjudgement of the second may result in adverse consequences. The inclusivity of the codes increased the sensitivity of the analysis, as primary care physicians may code for the same infection differently and there are

known variations in clinical practice; for example primary care physicians may code a consultation on the basis of symptoms (e.g. earache) rather than the diagnosis (e.g. AOM).

Construction of the complication diagnosis codes however were more focused on specificity rather than sensitivity, so that only relevant outcomes were included. For example, codes related to non-bacterial complications or an outcome unrelated to the infection pathways depicted in Figure 3-1 were not included (e.g. A551.00 Post-measles pneumonia, A021.00 Salmonella septicaemia would not have progressed from an index RTI). Similarly, codes which were likely to be inappropriate were omitted, i.e. complications related to healthcare interactions rather than the index infection (e.g. Read codes: H262.00 Postoperative pneumonia, H2C.00 Hospital acquired pneumonia, SP25400 Postoperative septicaemia).

The index diagnoses codes were grouped (Appendix 18) and classified as: acute otitis media (AOM), rhinosinusitis, sore throats, upper RTI, lower RTIs, viral RTIs, and total respiratory infections (total of all diagnostic codes excluding duplicated codes) (Table 3-1 includes definitions of infections). The primary index diagnostic codes were excluded if the coded term was indicative of a more complicated infection such as pneumonia, for which antibiotic prescribing may be recommended.

Complications assessed in this research included: mastoiditis, intracranial abscess, quinsy, scarlet fever, rheumatic fever, post-streptococcal glomerulonephritis, pneumonia, pleurisy, empyema, meningitis and sepsis (Table 3-1 and Table 3-2). As many of these outcomes are rare, a total complication variable was created to assess whether a patient had developed a complication or not. CPRD Read codes in full are provided in Appendix 18 and Appendix 19.

Table 3-1. Defining the a) index infections and b) complications, and corresponding infection duration

Index infection	Definition	Average infection episode duration	Ref
Acute Otitis Media (AOM)	An infection of the middle ear, with the presence of middle-ear effusion and a rapid onset of symptoms of middle-ear inflammation, such as ear pain, otorrhoea or fever. AOM is one of the most frequent diseases in childhood (<2 years, peak age 6-15 months).	4 days	178, 179
Rhinosinusitis	Inflammation of the sinuses and nasal cavity. Symptoms include nasal irritation, sneezing, facial pain or pressure, reduction/loss of sense of smell, rhinorrhoea (nasal discharge or congestion) and nasal blockage. Sinusitis is invariably accompanied by rhinitis, hence differentiation is no longer recommended. Most commonly caused by viruses, however symptoms may persist beyond 10 days when secondary bacterial infection occur.	2.5 weeks	179, 180
Sore throats	Sore throats and the infectious cause, pharyngitis, are generally self-limiting infections. Sore throats (including acute pharyngitis) are commonly assessed separately to upper RTIs due to this symptom alone being one of the common reasons for GP consultations.	1 week	52, 179, 181
Upper RTI	This category included coughs, general RTI symptoms and consultations for tonsillitis (inflammation of the tonsils). Symptoms of tonsillitis include sore throat, fever, enlargement of the tonsils, trouble swallowing, and large lymph nodes around the neck.	1 week	52, 179
Lower RTI (not including pneumonia-related codes)	This category included more severe lower RTIs such as coding for chest infections, acute tracheitis and bronchitis (but excluded pneumonia related CPRD codes).	3 weeks	179
Viral RTI	Common colds are self-limiting viral illnesses, with the following symptoms: rhinitis (not hay fever or allergic rhinitis), sore throat (not streptococcal pharyngitis), with or without fever, cough and/or productive sputum/purulent sputum. CPRD codes for influenza related consultations were also included in this category.	1.5 weeks	156, 179

Complication	Definition	Develops within	Ref
Mastoiditis	Mastoiditis is often a complication of AOM and is an infection of the spaces within the mastoid bone, a part of the side (temporal bone) of the skull, with puss spreading and forming a swelling/abscess behind the ear. In serious cases, the bone itself may become infected.	16 days	[182, 183]
Intracranial abscess	Also known as brain abscess, is a bacterial infection within the brain tissue, commonly associated with cerebral oedema (accumulation of fluid).	12 days	[182, 184]
Peritonsillar abscess (quinsy)	Peritonsillar abscess, also known as quinsy, is a rare and potentially serious complication of tonsillitis. The abscess (a collection of pus) forms between one of the tonsils and the wall of the throat. This can happen when a bacterial infection spreads from an infected tonsil to the surrounding area. Quinsy can occur at any age, but most commonly affects teenagers and young adults.	30 days	[126, 182]
Scarlet fever	Scarlet fever is an infection caused by Streptococcus pyogenes bacteria. The disease is characterized by a sore throat, fever, “strawberry tongue”, and a sandpaper-like rash on reddened skin produced by toxins released by the bacteria. It is primarily a childhood disease.	30 days	[182, 185]
Rheumatic fever	Rheumatic fever is an inflammatory disease which arises as a complication of untreated or inadequately treated “Strep throat” infection or pharyngitis, caused by Streptococcus pyogenes bacteria. Reactive antibodies cause an autoimmune response thought to impact the heart, skin, joint and the brain.	2 months	[52, 182]
Acute glomerulonephritis	Post-streptococcal glomerulonephritis can develop after pharyngitis or other Streptococcus pyogenes bacterial infections. This kidney disease develops after a skin or throat infection and develops not from the bacteria itself but from the body’s autoimmune response.	1 month	[52, 182]
Pneumonia	An infection of the lung parenchyma caused predominantly by Streptococcus pneumoniae (although can be caused by other bacteria, viruses and fungi). The infection causes swelling, inflammation and fluid build-up of the air sacs in the lungs.	28 days	[125, 186, 187]
Pleurisy	An inflammation of the pleura (the membrane which lies between the chest cavity and the lungs), characterised by sharp chest pains when breathing deeply, coughing or sneezing.	28 days	[186, 187]

Complication	Definition	Develops within	Ref
Empyema	Empyema is a collection of pus which collects in a body cavity, most commonly the space between the lung and the inner surface of the chest wall (pleural space) caused by an infection that spreads from the lungs.	18 days	[125]
Meningitis	A serious inflammation of the meninges, the thin, membranous covering of the brain and the spinal cord. Meningitis is most commonly caused by infection (usually viral or bacterial), although it can also be caused by bleeding into the meninges, cancer, diseases of the immune system, and an inflammatory response to certain types of chemotherapy or other chemical agents.	12 days	[184]
Sepsis/ bloodstream infection/ bacteraemia	Sepsis, also referred to as blood poisoning or septicaemia, is a life-threatening systemic inflammatory response triggered by an infection in the blood (i.e. the presence of a pathogen in the blood which causes symptoms). BSIs are defined as the presence of pathogen in the blood, which may or may not be symptomatic. Bacteraemia is the presence of a growth of viable bacteria from blood culture, patient may also be asymptomatic.	30 days	[187-189]

Table 3-2: Complication diagnosis groups, corresponding count of Read codes, ICD-10 codes and references utilised

	CPRD Read code count	ICD-10 codes	References (CPRD and ICD-10 codes)
Mastoiditis	100 codes	H68, H69, H70, H72, H73, H74, H75	133, 151, 183, 190
Intracranial abscess	See codes for meningitis	G06, G07, G08	191
Peritonsillar abscess/ quinsy	6 codes	J03, J35, J36, J39.0, J39.1	133, 151, 192
Scarlet fever	9 codes	A38	185
Rheumatic fever	20 codes	I00, I01, I02	151, 193, 194
Post-streptococcal glomerulonephritis	66 codes	N00, N01, N08	195
Pneumonia	94 codes (including codes related to pleurisy)	J13, J15-J17, J18	133, 140, 177, 187, 196, 197
Pleurisy	See codes for pneumonia	J90, J94.8, J94.9	140, 198
Empyema	17 codes	J85, J86	140, 197, 199
Meningitis	64 codes (including codes related to intracranial abscess)	A39, G00, G01, G03	187, 191
Sepsis/BSI	65 codes	A40, A41.0, A41.1, A41.2, A41.4, A41.5, A41.8, A41.9, A42.7, A49, R65.2, B95, B96, B99	187, 189
Symptoms and signs involving the circulatory and respiratory systems	N/A	R00-R99 [Vague ICD-10 codes referring to symptoms and signs rather than definitive primary diagnosis for hospital admission. These codes were included in the initial data management steps.]	All R-codes initially included.

All primary care CPRD Read codes (for index diagnoses and complications) can be seen in Appendix 18 and Appendix 18, these were too numerous to include in this table. Complications assessed in primary care, particularly for rheumatic fever, glomerulonephritis, empyema, intracranial abscess and meningitis, were very rare and trends for these infectious outcomes were not assessed separately. Further ICD-10 detailed codes can be seen in Appendix 20.

3.3.4 Selection and grouping of ICD-10 codes

As mentioned, ICD-10 codes are a comprehensive classification of causes of morbidity and mortality used for coding within HES and ONS. A similar strategy as was taken for Read codes was implemented to identify and construct relevant ICD-10 code lists. A rapid literature search was completed using PubMed and the Clinical Codes repository website (https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/articles/) to identify previous studies which had utilised and published supplementary ICD-10 codes related to the outcomes (Figure 3-1, Table 3-2).

These text strings and code stems were then searched for in the NHS current National Clinical Coding Standards reference lookup tables acquired from the NHS Digital Technology Reference Data Update Distribution (TRUD). The resultant ICD-10 classifications were an update of any ICD-9/historic terms or codes found in the literature and included any relevant additional ICD-10 codes.

The codes were discussed and reviewed by a practicing clinician, with the lists assembled included in Table 3-2 along with relevant references. The codes for complications were grouped in the same way as Read codes, i.e. into: mastoiditis, intracranial abscess, quinsy, scarlet fever, rheumatic fever, post-streptococcal glomerulonephritis, pneumonia, pleurisy, empyema, meningitis and sepsis (Table 3-1 and Table 3-2, with more detail in Appendix 19), along with a "total complication" variable.

3.4 Data management, linkage and processing

This section describes how the different data sources were processed and linked. Data for patients with an initial uncomplicated RTI were extracted, antibiotic prescriptions were identified, an infection episode was created, and linked to any subsequent complications that developed (including death).

STATA version 14 (STATA Corp, College Station, TX, USA) was used to perform the data management.

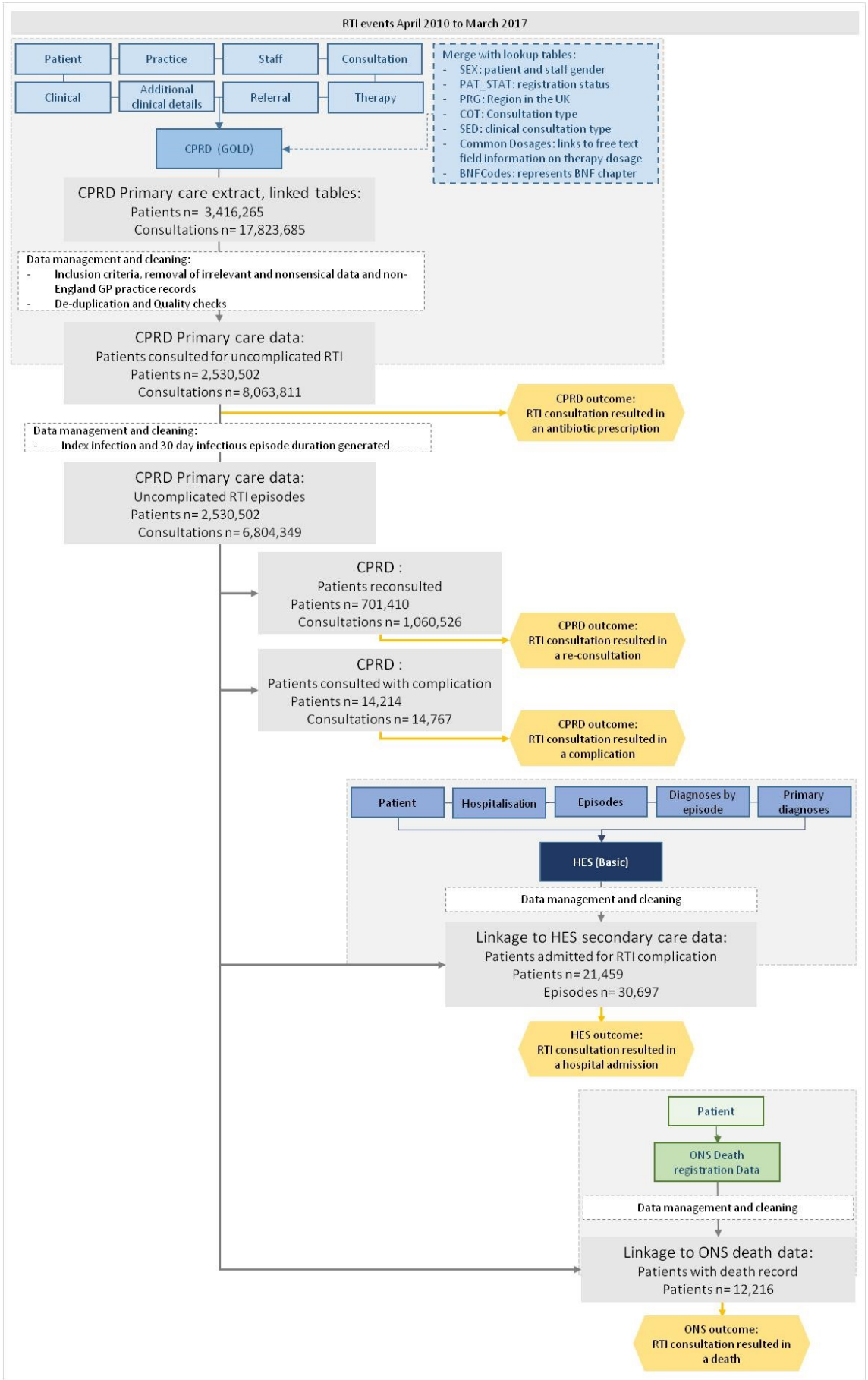
3.4.1 Data management of CPRD data

The data structure of the CPRD patient-level records were arranged into several files (also known as tables) relating to their primary care, eight of which were linked to provide an overarching depiction of care per consultation across the study period (Figure 3-2, Appendix 21 provides details of the different tables and a graphical representation of linkage across the files). Linkage within CPRD used a combination of the following variables: patient ID, staff ID, consultation ID, practice ID (obtained from the last 3 digits of the patient ID). A large combined file was then provided by the data manager (Appendix 22 provides the details of CPRD variables retained), to which all the data processing was applied and where relevant look-up files were also subsequently linked, to provide information such as: patient gender, registration status of the patient, region of the practice, consultation type, BNF codes (Figure 3-2).

All fields were formatted (e.g. date fields converted into date format) and labelled where codes had been used (e.g. region was coded as numerical values initially). Additional necessary fields were also generated, including:

- Country using the regions code (11, 12, 13 represented Northern Ireland, Scotland and Wales, the remaining codes were amalgamated for England)
- Age calculated using the year of birth field [yob] and consultation year ([cons_year] which was produced from the consultation event date)
- Age groups were created using this generated age field
- Time points were created so as to attach consultations to the trend line in the ITS analyses, [year] and [month]
- Clinical Read codes were grouped; (please refer to section 3.3), into: Acute Otitis Media, Rhinosinusitis, Sore throat, upper RTI, lower RTI, viral RTI, and a separate RTI infection total group was created.

Figure 3-2.The linkage process within and between the different data sources: CPRD, HES and ONS



3.4.1.1 Data management: Data inclusion/exclusion criteria

The study population included all patients who had an initial consultation for an uncomplicated RTI (Appendix 18 for the Read code list which defined this cohort) within the study period of April 1st 2010 (later changed to April 2011 due to changes made in ICD-10 codes in January 2011 and due to unreliable trend data in financial year 2010. Please refer to section 3.3.4 and 3.7.2) to March 31st 2016.

CPRD applies data quality markers at patient and general practice level. A patient's record is considered to be acceptable for research quality where there is consistency with regards to age, sex, registration, event dates, and the patient has been permanently registered with the practice (although transfers between practices can occur).[173] General practice data are considered of acceptable quality following the assessment of data completeness, plausibility and continuity of care, an "up-to-standard" date is then given when the data are deemed reliable.[173] The data used included general practices in England that were classified as "up to standard" (UTS) prior to or on the date of the index RTI consultation date. Patient records were included if the data quality was classified as CPRD-acceptable (Appendix 22 contains the variable details and definitions). Data for these individual patients were included throughout the study period, or until the date of transfer of a patient to another general practice, date of death or the date at which the practice had its last collection (Figure 3-2 and Appendix 23 provides details of the number of records retained and excluded).

Patients who were temporarily registered with a GP were excluded to avoid duplication of data, as these patients may have been permanently registered elsewhere. Permanent registration was defined based on a patient having a "continuous" registration status, as well as patients having a current registration date that was the same or dated before the consultation event date. Patient records were retained where patients had a registration period extending 30-days post RTI consultation event date, which was essential for complete follow-up and measurement of potential unintended complications.

The consultation event date (obtained from the CPRD consultation table) was the date used throughout the research to identify the date of consultation and the duration between different and

subsequent consultations (when assessing re-consultations or consultations for complications). The Clinical, Therapy and Test tables also contained event dates, which refer to the day on which that event occurred. These event dates were not exclusively the same as the consultation event date and could have been entered retrospectively, or were in certain instances blank. To account for this variation between potential dates and any clinical mismatches, a 60 day buffer was created; clinical event dates which varied by 60 days or more from the consultation event dates were not included. These were thought to predominantly be patient records which had a delay in entry onto the system, or were transferred/newly registered patients who had their historic data entered, or were erroneous and therefore unreliable.

3.4.1.2 Data management: De-duplication and Quality checks

Various steps were taken to de-duplicate entries (e.g. numerous duplicate entries were for admin entries rather than face-to-face consultations). A variable which identified consultation type was reviewed, to identify whether records should only include "surgery consultation". However, this type of consultation (which does not include home visits, emergency consultations, clinic consultations etc.) accounted for approximately 80% of the consultations alone, prior to de-duplication. Records were not limited to this type of consultation as the majority of irrelevant consultation types (e.g. "Mail from patient", "Data not entered") were removed via de-duplication. With uncertainty of completion and accuracy of this field, it was used during the de-duplication steps but no further.

Although CPRD applies data quality markers, a handful of records were removed due to nonsensical data (e.g. Same patient ID, consultation, and consultation date with either different genders (not including indeterminate gender, as patients may have changed genders or infants may not have this labelled yet) or date of birth).

A final deduplication step was based on patient ID and consultation date. The consultation ID variable did not necessarily uniquely identify a consultation. A patient [pat_id] within the same day [consdate]

may have another consultation (different [consid]). Rarely these consultations were for unrelated different Read codes, although more often the records appeared to be for the same consultation. Only one consultation per day was retained, which would have removed patients who may have legitimately re-consulted on the same day for similar diagnoses. However, these were assumed errors and were uncommon. Similar methods have been used in the published literature and thought to be extremely unlikely to have impacted the results, but if so, would have underestimated effects rather than overestimated.

3.4.2 Identifying antibiotic prescriptions

Drug codes that map to section 5.1 of the BNF were translated into CPRD product codes and used to link the lookup product table (explained in section 3.3.1). All prescriptions for antibacterial agents (excluding anti-tuberculosis and antileprotic drugs) within the study period were linked to patient consultations if both occurred on the same date, all other therapies prescribed were excluded. A variable was created to identify broad-spectrum antibiotics.

3.4.3 Creating an episode of infection

To assess the outcomes of re-consultations and an infection which has progressed in severity, an episode of acute infection was defined per patient for each consultation/record.

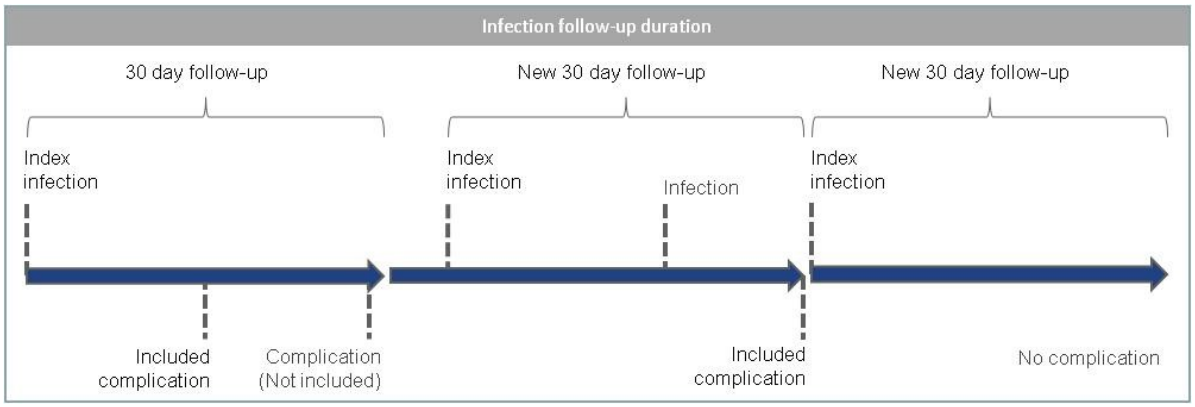
Following a rapid search of the published literature for the duration for which patients were commonly followed-up (Table 3-1) and the defined durations of an infection episode (i.e. the average days/weeks required before a patient recovers from an infection or develops a more severe outcome), the findings were incorporated with clinical input from a practicing GP, to identify an all-encompassing duration to be used. A 30 day follow-up duration was thought the most reliable in providing enough follow-up days to ensure outcomes related to the index infection were captured, but not too long a duration that any

outcomes seen would be unrelated (Table 3-1 provides the published durations). Table 3-1 presents various durations within which index infections may resolve or progress. It was deemed more effective to apply a longer duration in order to capture more severe complications, such as sepsis, which often take on average 28 days to 30 days (60 days has been reported for bacteraemia/sepsis in certain studies) to manifest as a treatment failure of an initial uncomplicated infection.

The episode start date (index date) was defined as the date of the first uncomplicated RTI consultation within the study period for each patient. If there was more than 30 days between that and another RTI consultation for the same patient, the later consultation was attributed to a new RTI episode. Consultations within the 30-day period were considered relapses and re-consultations for unresolved index infections (Figure 3-3). Where a re-consultation or complication occurred on the same date as the episode start date, this outcome was excluded from analyses. Similarly, all hospital admissions or deaths which occurred on the same day as initial primary care index consultation were not included as outcomes. As the analyses were attempting to identify treatment failures it was deemed that these same-day outcomes were not related to the decisions made in primary care on that day, as to whether the patient was prescribed an antibiotic or not, or to the QP, but may be more related to the severity of the patient's infection.

In order not to duplicate or inflate outcomes, if more than one complication occurred within the 30-day duration, only one outcome was included for the same episode of infection, i.e. complication was assessed as binary per episode; whether that episode resulted in a re-consultation/complication or did not. This was the case when assessing overall complications, however separate outcomes were assessed by diagnostic group e.g. a patient could not have had two pneumonia outcomes in one episode, but could have an outcome of pneumonia and BSI if subsequent primary care consultations or hospital admissions within 30 days was indicated as such.

Figure 3-3. Depiction of episodes of infection (30 day duration)



3.4.4 Linking CPRD index cases to CPRD consultations of complications

The index CPRD uncomplicated RTI consultation was linked to the CPRD Clinical and the Referral file, to identify whether the same patient had a clinical or referral record within 30 days post index consultation date as denoted by a READ code for a complication. The Referral file was used in addition to the Clinical file, as this contains details of patients being referred to external care centres, usually to hospital for inpatient or outpatient care, and hospital discharges.[51] As several of the complications assessed are rare and as the complications are more severe and may require secondary care, using both tables increased the sensitivity of being able to identify complications that developed from infections seen in primary care.

3.4.5 Data linkage methods

A subset of the CPRD contributing English practices consent to participating in the CPRD linkage scheme, this is approximately 75% of English CPRD practices (approximately 58% of all UK CPRD practices).[164] Each practice consents to have their data linked for research purposes via an independent third-party (NHS Digital) to external data sources. Individual patients also have the right to opt-out.

Other than eligibility to link, if the patient resides outside of England or does not have a valid NHS number identifier then linkage to the HES and ONS records of these patients would not be possible.

Patient identification (ID) numbers from the data managed CPRD RTI data were extracted. The CPRD source file (linkage_eligibility.txt) was then merged with to identify patients from English practices that had consented to take part in the linkage process (variable names: [hes_e] or [ons_e]) at any point during the study period. This linkage coverage file defines the time period each linked data source covers [start, end]. Those patients not eligible for the infection episode duration were removed, and the remaining patient IDs were sent to the CPRD team who coordinated the NHS digital linkage process. Linkage between CPRD and HES, and CPRD and ONS uses an eight-step deterministic linkage algorithm described in Appendix 24.

3.4.6 Returned linked HES and ONS records

The CPRD extract sent for linkage and the number of patients included in the extract was too large for the customary CPRD linkage process. Due to this limitation in the size of the data which could be linked, ICD-10 codes of the complications of interest were provided alongside the patient IDs. Hospital admission records of all patients who had had an ICD-10 code during their hospital admission spell for the complications of interest were returned. In HES, a spell of care, alternatively known as hospitalisation, is defined as the period from the date of hospital admission to the date of discharge (i.e. this can include many episodes; episode in the HES data is defined as the period of activity for a patient under one consultant within one healthcare provider, i.e. a patient would have a different episode if transferred to another consultant). For patients who had a hospital admission for a complication, the returned file included every hospital admission spell ICD-10 codes and all previous hospital admission records, which permitted assessment of whether a patient had been previously admitted into the same or a different hospital.

Although the CPRD data were linked to other datasets, the outcomes were assessed separately for complications seen in each data source. Linkage of outcomes across all settings combined would have increased internal validity and ensured cases were not missed within each setting, however in so doing reducing the sample size as only those CPRD patients eligible for data linkage would be included. Hence, outcomes in primary care, secondary care and mortality data were assessed separately. This enabled the assessment of complications by severity, maintained the larger sample size when assessing primary care reported outcomes, and consequently the power and generalisability of the results, thus providing a more precise evaluation compared to assessment of unlinked single databases.[165]

3.4.7 Linking CPRD index cases to HES records

The HES tables provided by CPRD did not follow a typical HES format, the data were split into separate tables which were reformatted, labelled and linked together. A patient may have had more than one HES hospitalisation (/spell), the first spell within 30 days (not including admissions on the same day as primary care consultation) were retained and subsequent spells were not included if the ICD-10 code was for the same outcome category within episode (i.e. multiple hospital admissions within RTI infection episode of 30 days were de-duplicated, thus the hospital admissions outcome when assessed was only accounted for as a having occurred or not within the RTI episode).

The published literature using HES hospital admission varied in terms of the codes used. Certain studies used the primary and all diagnoses codes within the first episode,[177] others assessed all diagnoses in the first episode,[200] or just the primary diagnoses in the first episode,[201, 202] while some used the primary diagnosis in the first episode along with the primary diagnosis in the second episode.[203] The analyses undertaken used the primary diagnosis code and all first episode codes.

The primary ICD-10 code recorded in HES represents the initial diagnosis for which the patient was admitted for their first spell and the first episode within that hospital admission. Where the primary ICD-10 diagnosis code for the first episode of a spell was related to 'symptoms and signs' i.e. unspecific vague codes related to symptoms, signs and abnormal clinical and laboratory findings, these were replaced with the primary diagnosis code of the second episode within the same spell. These codes begin with the letter "R" (termed R codes), and predominantly refer to vague symptoms such as "R50.9: Fever, unspecified", although certain codes found refer to outcomes of interest e.g. "R65.2: Severe sepsis", "R78.81: Bacteremia". If a second episode did not exist within that same spell or the primary diagnosis for the second episode was also a code referring to 'symptoms and signs' then the primary diagnosis from the first episode was retained. The rationale for this was that patients with a severe infection would either be classified as that diagnosed on admission and within the first episode or would have been admitted for a period long enough to have undergone microbiological investigation to determine if the infection was of bacterial aetiology; in this way the subjective clinical diagnoses based on signs and symptoms were replaced with a diagnosis of a confirmed bacterial infection during the second episode. A similar R-code rationale has been utilised within data processing steps for published national statistics.[204]

The main assessment utilised all first episode diagnosis codes. Although all the codes within the first episode may not have been recorded immediately at admission, they permitted the assessment of patients who may have been admitted for multiple reasons e.g. pneumonia and bacteraemia, and for findings which are not often coded as the primary diagnosis in the first episode of a spell. As certain outcomes are rare, it was thought that assessment of complications using all the listed codes for the first episode within the first spell was more reliable and sensitive. Furthermore, by including a wider code list this also corrected for any changes in coding guidelines.

Similarly to the data processing undertaken for the primary diagnosis, R codes were also utilised here. Where the primary ICD10 code for the first episode of a spell was an R code, the second episode

diagnosis codes were used to replace the first episode codes where a second episode within a spell was present and where the primary diagnosis code of the second episode was not an R code.

The combined HES table extract was then linked to the index CPRD RTI consultations. The 30-day follow-up duration which had previously been created in the CPRD data was used to identify whether the hospital admissions were within the infection episode duration. Duplicate hospital admissions within the 30 days were not recounted. Patients who were admitted to hospital on the same day as the index primary care consultation were removed, as it was thought that the admission into hospital was unrelated to whether the patient received antibiotics, therefore unrelated to the QP, and/or that the patient may have been referred by the GP to the hospital.

To ascertain that the HES complications assessed were related to the primary care consultation and not due to other health care interactions (i.e. previous hospital admissions), records and outcomes were removed if the patient had a recorded hospital admission (for an unrelated ICD-10 code) within the RTI infection episode (including the day of primary care consultation) prior to the complication (not including the admission date i.e. if the previous hospital admission was the same date as the outcome hospital admission date, these were likely to be transfer cases and were retained).

3.4.8 Linking CPRD index cases to ONS records

The ONS patient data are provided in one table which contains the following main variables used: a patient ID which was used to link back to CPRD data; a unique ID assigned to patients in the death registration data [gen_death_id], date of death; a partial date of death where the exact date of death was not known; date of registration of death; primary cause of death which is defined as the underlying cause of death; further 15 causes of death variables; additional 8 variables for causes of neonatal deaths.

The following quality checks and processing were completed:

- Where the date of death registration field was complete and the date of death field had missing data, the date of registration was used
- Records where the date of death registration were before the dates of death were removed
- The [gen_death_id] field is a unique ID for each patient. Where a patient contributed to more than one CPRD practice they will have the same [gen_death_id], these duplicate recordings of deaths were removed, based on RTI consultation date

Deaths within 30 days were retained when the ONS mortality records were linked to the CPRD index infection. All-cause mortality was assessed (not including the day of primary care consultation), as this captured mortality for events which could have precipitated the outcomes of interest, particularly in the older population (e.g. stroke, myocardial infarctions following a bout of pneumonia).[186] Sensitivity analysis were undertaken to assess mortality related to the ICD-10 codes for complications (with similar R code replacement completed as the HES data).

3.5 Outcome measurements and denominators

Although patient level data were used, these were aggregated to establish an England rate, and this was the level of analysis used for the time series analyses. The unit of observation is at an aggregate ecological level rather than at an individual level, albeit prescriptions and complications were extracted based on individual patient level linkage.

The main outcomes assessed were:

- Primary care antibiotic prescriptions on the same day of RTI consultation: estimated as monthly antibiotic prescription rates (measured as antibiotic items) per 1,000 RTI consultations for all CPRD included practices in England.

- Re-consultations for uncomplicated RTIs within 30 days: estimated monthly rates per 1,000 registered patients
- Complications where patients developed a subsequent severe infection within 30 days and consulted in primary care for specific outcomes of interest: monthly per 100,000 registered patients
- Complications where patients developed a subsequent severe infection within 30 days and required hospital admission for specific outcomes of interest: monthly rate of hospital admissions for complications per 100,000 patients (eligible for HES linkage)
- All-cause mortality within 30 days of an index RTI consultation: Rate calculated per 100,000 patients (eligible for ONS linkage)

The registered patient rates were calculated using the denominator of all registered patients contributing acceptable quality data, in up to standard general practices, to CPRD during the study period. The CPRD denominator files (3 separate files) provide information on the entire population of patients and practices in the data and the subset of patients (acceptable and up-to-standard). Two of these files were linked: the "All Practices" file which provided the general practices last collection date and the regions, to the "Acceptable patients from UTS practices" file to obtain the number of registered patients in UTS practices. To link the files, the practice IDs were identified using patient IDs; the last 3 digits of the patient ID equates to the general practice ID. The region field was used to identify and retain all the practices in England. Two fields were created to identify whether patients should be included in the denominator count for the period assessed; a "patient exit date" specified the date on which the patient exited CPRD observation, this took into consideration when the general practice last contributed data (last collection date), the date the patient left the practice (transfer out date) and if the patient had died. A "patient entry date" was created which specified the date the patient entered observation, which took into account the date the practice started returning UTS data, when the patient joined the practice (current registration date and the birth date of the patient (generated from [birthmonth] and [birthyear]).

Whilst assessing the registered patient counts of the denominator data, prior to its use in calculations, as well as whilst assessing the RTI consultations and episode data, it became evident that the East Midlands region had stopped fully reporting in July 2014. Further investigation as to this region's lack of data revealed that the decrease in RTI consultations during this period for this region was likely due to a decrease in practices using the Vision system. The Vision system lost market share over the previous few years, with a shift to EMIS (another software system used, refer to section 3.1.1) and CPRD had seen a related drop in the number of actively contributing practices. This change in reporting would have skewed counts of consultations, episodes, prescriptions and outcomes, however this reduction would not have impacted calculations of rates. In fact, using the denominator file to calculate rates was necessary to ensure such change and shifts in reporting due to changes in systems used, did not impact the findings.

To note, when calculating rates for outcomes of hospital admissions (HES data) or mortality (ONS mortality data) the denominator included registered patients within UTS general practices who were eligible for linkage.

3.6 Quasi-experimental designs and what approaches could have been used to identify the effect, if any of the Quality Premium

The QP was implemented nationally in England from April 2015. As this research aimed to evaluate the effects of what was a national intervention, no control group was available, precluding the option of undertaking a randomised controlled trial (RCT). With access to retrospective data and a sample large enough to detect expected effects with robust data on exposures, outcomes (including potential rare outcomes, which would require participant numbers too large for a RCT to be feasible) and potential confounders, a natural experiment was the strongest approach. A defining feature of a natural experiment or quasi-experiment is that it is not possible to manipulate the exposure to the intervention.[205] A quasi-experiment makes use of pre-existing observational data and does not succumb to difficulties in low external validity faced when using RCTs; as these trials often have stringent inclusion criteria, participants and experimenters may behave differently under the knowledge of being involved in an experiment, and the settings and participants tend not to be representative of the wider population.[206]

Quasi-experimental designs can be categorised into: designs that use a non-randomised control, designs which have a pre-post comparison, and designs which incorporate trends in the assessment of the outcome (designs may however fall into more than one of these categories). Designs that use a control are utilised where randomisation of participants is not possible, and the intervention has been targeted at or introduced within a particular population, an unexposed population is then used as a comparison group.[205-207] As no pre-intervention data are utilised in this design, it is not possible to assess whether the outcome was already different between the two groups. Limiting the analysis to a pre-post design on the other hand, may over-estimate any impacts of the QP, as the trend in antibiotic prescribing was already decreasing pre-QP and the (unknown) trend in complications may have been increasing. Using a pre-post comparison (also known as a pre-test-post-test or before-and-after design)

assumes the outcome of interest would remain constant in the absence of the intervention and compares observations at one or more points in time pre-intervention to time point(s) post-intervention.[205-207] Differences in the outcome are then associated with the intervention effects. This design, when only comparing one point pre- and one point post-intervention, is prone to large threats to validity as there may be numerous explanations for the changes seen in the outcomes measured, such as random fluctuations, or an already existent pre-intervention decreasing or increasing trend, hence effects observed may be an extension of what was occurring regardless of the intervention.[205, 206, 208] Difference in difference analysis, a combination of non-randomised and pre-post comparison designs, which takes into account pre-existing differences in the two groups, was not used due to the threats of validity stated. Regression discontinuity design is an example of an approach which incorporates trends in the outcomes according to a variable. Interrupted time-series (ITS) is considered a form of regression discontinuity design whereby the variable is time, and is also considered a pre-post comparison, although it uses an analysis of trend.[205] The pre-intervention outcome trend is extrapolated post-intervention, across time, to create a counterfactual, and the regression line modelled is then compared to this counterfactual to assess whether there is a discontinuity in effect, as measured by a change in the level or slope. Segmented regression is the statistical method used to partition the trend line into intervals, based on the time at which the intervention being assessed was introduced, so as to measure any potential level or slope differences.[209]

3.7 Modelling impact of the QP, using segmented regression of interrupted time series

A time series refers to repeated continuous observations made on the same variable over regular spaced intervals of time. An interruption to a time series occurs when it is segmented into two or more defined portions around a change point; a point at which we expect to see a change in the time series due to an identifiable intervention, event or policy change, introduced at a clear point in time.[209]

Segmented regression of an ITS allows us to perform statistical modelling by measuring the trend in the observed first segment (prior to the intervention) and the second segment (post-intervention) and comparing the differences to the expected trend had the interruption to the series not occurred. Had the QP not been implemented, we would hypothetically expect to see a continuation of the pre-QP trend. The extension of this pre-intervention trend line is known as the 'counterfactual', and is used as the 'control', to compare the observed post-intervention trend line. This method of segmenting a time series permits us to identify i) whether there was an impact, and ii) the degree and direction that the intervention affected the outcome of interest (i.e. prevalence of antibiotic prescribing or unintended consequences/complications), immediately and over time. More formal conclusions regarding the intervention can be made by using statistical modelling to estimate: i) the pre-intervention trend, ii) the change in the trend post-intervention (also known as the slope or drift), iii) the change in the level at the intercept (i.e. when the QP was introduced, April 2015).[206, 209, 210] If the intervention did have an impact, there would be a variance in the trend and/or level of the series at that particular point in time and a statistically significant (p<0.05) "interruption" in the trend would be observed (Figure 3-4).[206, 210]

3.7.1 Segmented regression of interrupted time series method used and related formula

A monthly time series of the outcomes assessed, from April 2011 (initially April 2010) to March 2015 was used to establish an underlying trend, which was 'interrupted' by the intervention of interest, the QP on 1st April 2015, producing two segments, pre- and post-QP, to assess whether there was a coinciding change in the trend or level of the outcomes. The modelling and statistical tests were undertaken using R Studio (http://www.r-project.org).

The implemented segmented regression models were fitted using a least squares generalised linear regression (GLS) line to each segment, thus assuming a linear relationship between time and the

outcome assessed i.e. antibiotic prescription rates or complications.[209] Antibiotic prescriptions for RTIs, RTI infections and consultations, are known to demonstrate cyclical seasonal/monthly fluctuations. There are two complications of analysing seasonal data which could introduce bias, the first being that there may be an uneven distribution of particular months pre-intervention compared to the post-intervention series (e.g. if there is a higher quantity of winter months included in the pre-intervention compared to the post-intervention, these would usually be months with higher antibiotic prescribing and RTI complications).[211] The second potential bias is that of serial dependency, whereby consecutive temporal observations are likely be more similar or closely correlated to neighbouring monthly observations within the same time of year, rather than months further away (or to observations which are two, three or more lags away), leading to what is known as autocorrelation.[206, 211, 212] There may also be seasonal patterns in monthly time series data, for example where prescribing in one month of the year is more similar to prescribing in the same month in the year before than to prescribing in any other month of that year/adjacent months.[209] To model long-term seasonal patterns, data were time stratified by month[213] (discussed in more detail further on), this permitted adjustment of confounding by seasonality. To account for autocorrelated data, an autoregressive moving average (ARMA) model using the monthly-stratified segmented regression was fitted.[214] ARMA and an autoregressive integrated moving average (ARIMA) models are widely used methods for time series modelling.[215] ARMA is a combination of autoregressive AR (p) and moving average MA (q) linear time series models. The ITS ARMA regression models used assume the following form (this is further visually expressed in Figure 3-4):[216]

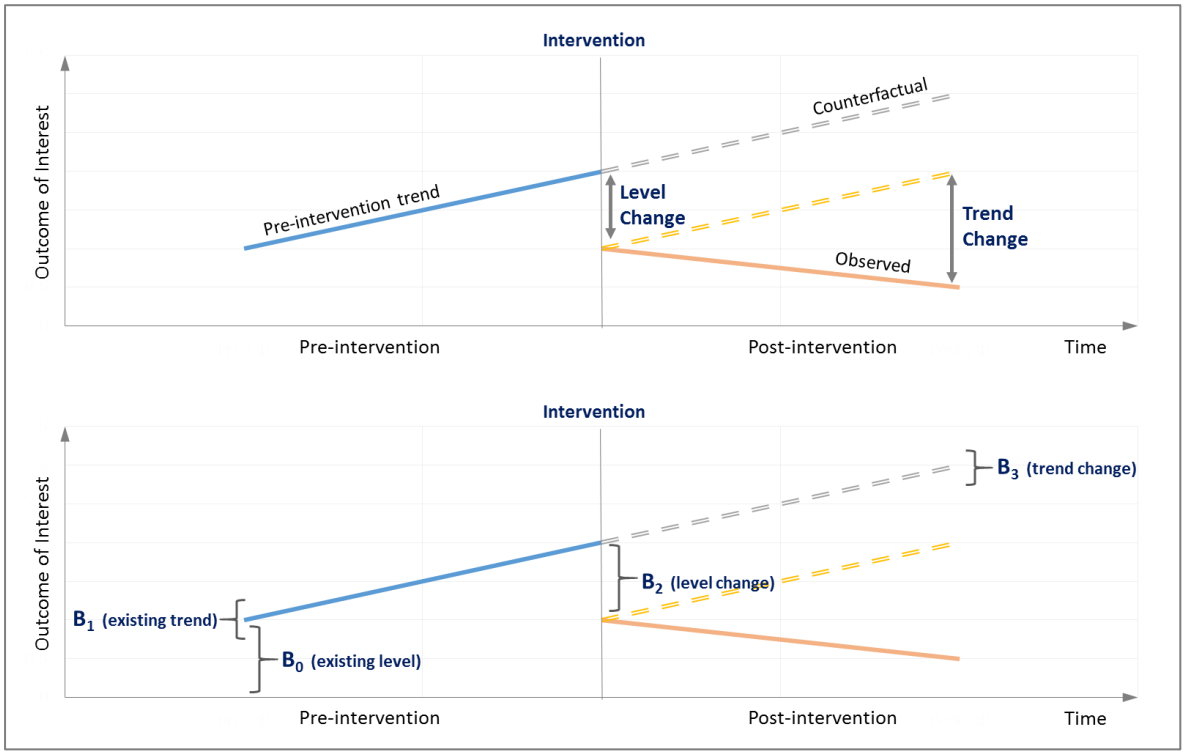
$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \varepsilon_t$$

Where:

- Y_t is the aggregated outcome variable measured at equally spaced time point t. Throughout modelling using ITSA the assessment of outcomes has been by month
- T_t is a continuous variable indicating time (in months) since the start of the observation period

- X_t is an indicator variable of the intervention (pre-intervention period was coded as 0 and the post-intervention as 1)
- X_tT_t is an interaction term of X_t and T_t, which starts in the observation period immediately after the introduction of the intervention (QP) and runs sequentially starting from 1 until the last observation
- β_0 estimates the intercept, or the existing level of the outcome variable at the beginning of the observation period (i.e. baseline level of the outcome at time zero).
- β_1 estimates the trend/slope prior to intervention, which is the trajectory of the outcome variable until the introduction of the intervention
- β_2 estimates the change in the level in the outcome that occurs in the period immediately following the introduction of the intervention (compared to counterfactual)
- β_3 estimates the difference between pre- and post-intervention trends/slopes of the outcome

Figure 3-4. Graphic illustration of the concept of an interrupted time series analysis design and the underlying formula



Legend: *The time series depicted shows the impact of the intervention to be a step decrease in the level (β_2) and a decrease in the slope (β_3), compared to the counterfactual.*

Estimates of the pre-QP trend, the change in the trend post-QP and the change in the level immediately after the implementation of the QP are the model outputs which provide statistical evidence as to whether there was a change in the outcomes assessed (decrease in antibiotic prescribing or an increase in complications) at the time interval at which the QP was introduced. The model estimates were then used to quantify the absolute change and relative change at 12 and 24 months.

The absolute change was defined as the difference between the predicted model value (at 12 months and 24 months post-QP) and the estimated value had the QP not been implemented (the counterfactual value at 12 months and 24 months).[209] The absolute change informs as to whether the predicted value was different at a time point past the start date of the intervention and informs on whether that value increased or decreased. (Absolute change= predicted value at 12/24 months – counterfactual at the same point in time).

The relative change, expressed as a percentage, was defined as the ratio of the predicted model value to the counterfactual value.[209] (Relative change= [predicted value at 12/24 months – counterfactual at the same point in time]/ counterfactual at the same point in time).

3.7.2 Model building, diagnostic checks and final model selection

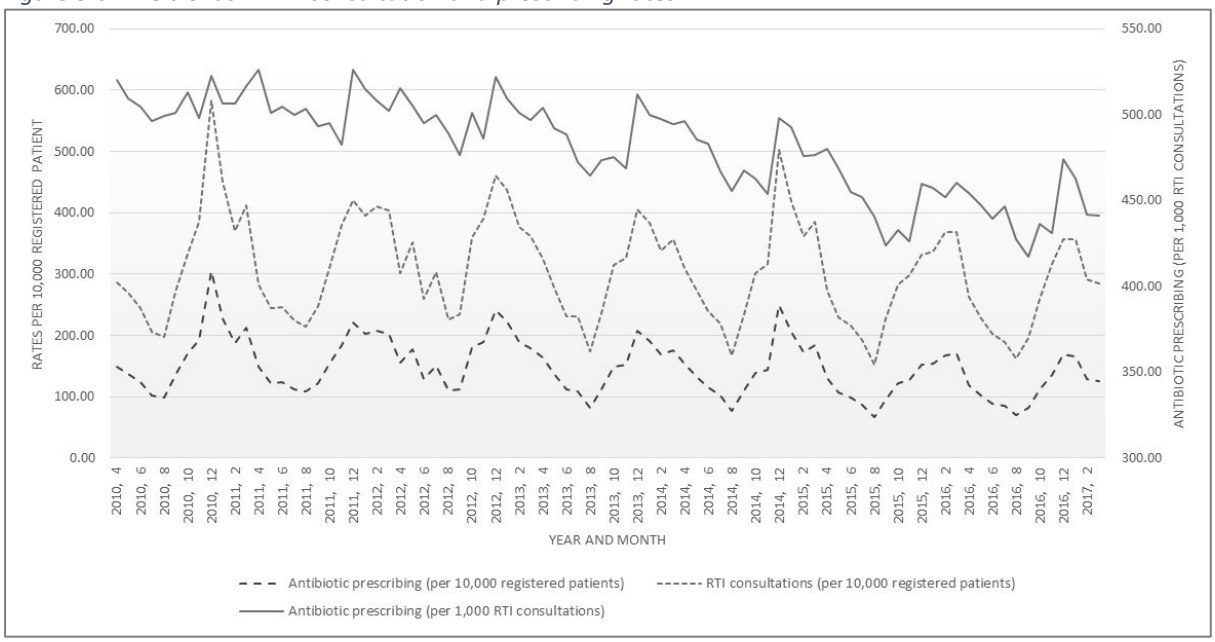
There are four fundamental phases in the construction of an ITS ARMA model: identification; model selection and estimations; diagnostic/model fit testing and correcting; and specifying the final model to produce required estimates.

The data were first examined in order to identify the most suitable model to fit and to uncover the general patterns in the data. The trend was assessed using a scatter plot for visual inspection of the time series, summary statistics of the data were tabulated to assess before- and after-outcomes. This provided an indication as to how stable the pre-intervention trend over time was prior to the QP. Moreover, this permitted assessment of whether linear models would be appropriate, whether there were apparent seasonal trends which would need to be incorporated into the model build, whether there were any irregularities in the data which should be investigated further as potential outliers or wild points, and whether any instability in the series may be due to data quality issues.[209, 217] As the ARMA model fits linear segments, non-linearity would need to either be "differenced" (converting the ARMA model into an ARIMA model, which includes this differencing), or a linear transformation would need to be performed, or the time series period may need to be adjusted if a section (which is not directly pre- or post-intervention) demonstrates curvature or appears irregular.

The study period initially spanned from April 2010 to March 2017, however after assessment of several pre-intervention trends it appeared that data spanning the financial year 2010/11 appeared inconsistent relative to the remaining data; seasonal patterns for that year were also different to the following years (Figure 3-5). Completing an ITSA requires a pre-intervention period long enough to

provide enough data to model the trend. However, where the period is very long, there is a risk that the trends may have historically differed from the more recent/current trends (e.g. due to changes in data collection or coding procedures), which would raise doubts about the validity of the comparison.[218] During inspection of the data, it became evident that antibiotic prescribing trends in financial year 2010/11 did not follow the seasonal variations seen in the ensuing years (Figure 3-5, prescribing rate per 1,000 RTI consultations). This variation in trend in FY 2010/11 compared to the years following could be due to the remnant effects of the influenza outbreak in 2009/10, which may have resulted in greater RTI consultations and antibiotic prescribing seen in 2010 (Figure 3-5).[219] Greater consultations in general practice could be due to increases in RTIs and requirement for medical care, or due to increased patient anxiety in the winter of 2010, particularly in December, as well as the potential influence of the public guidance to seek health advice if experiencing respiratory or flu-like symptoms.[219] Similarly, the antibiotic prescribing peak seen in December 2010 could either be due to greater diagnostic uncertainty triggering inappropriate prescribing for viral RTIs in response to the greater consultations, or due to appropriate antibiotic prescribing to treat co/secondary bacterial infections due to pathogens such as *Streptococcus pneumoniae*.[220, 221] The potential influence of the influenza epidemic 2009-10, the risk of less reliable coding in historical data, and updates made to ICD-10 codes in January 2011, may all have impacted on the assessment of complications during this time period. The data for financial year 2010/11 were therefore treated as an anomaly, as the inclusion of this period may have skewed the pre-intervention trend and impacted on the accuracy of the ITS models. Data from 2011/12 onwards was therefore used throughout the analyses. This remaining data duration was more than sufficient to model trends and seasonal effects as the usual requirement for an ITS are three measurement points pre- and three post-intervention,[208] with the recommendation when evaluating seasonal variation is extended to twelve time points pre- and twelve post-intervention.[209]

Figure 3-5. The trends in RTI consultation and prescribing rates



All the outcomes assessed exhibited seasonal variation, where this is not controlled for in the regression models this time-varying confounder may account for the fluctuations seen in the outcomes. There are numerous ways in which seasonality can be addressed. One such method is to use periodic functions (also known as Fourier terms or harmonic terms) which can be fitted into the regression model. These are pairs of sine and cosine functions of time which model seasonal variations in the outcome as waves with peaks and troughs throughout a year, with these peaks and troughs being guided by the inputted data.[213] Another method is to expand the flexibility of these waves or splines by including additional sine/cosine pairs, in so doing decreasing the wave lengths and incorporating more peaks and troughs. Using periodic functions will model smooth trends, however the modelled seasonal pattern is forced to be the same every year and may not reflect the pattern of the data well, and is also mathematically more difficult than using a time-stratified model.[213] A time-stratified model was used to adjust for seasonality throughout the analyses, as long-term patterns are known to be frequently captured well using this method.[213] This method splits the study period into intervals, months in the analyses undertaken, with the inclusion of indicator variables for each time interval/month in the ARMA model.[209, 213] As a sensitivity analysis, the amount of control for

seasonality was tested using quarterly time-periods, however monthly time-stratification produced better fitting seasonal data compared to the quarterly seasonal adjustments and were therefore preferred.

Provisional standard linear regression models with time series specification were produced, which were time stratified for seasonality in months. These were assessed for any residual autocorrelation using the 2-sided Durbin-Watson test, visual inspections of plots of residuals against time, and visual plots of the autocorrelation (ACF) and partial autocorrelation (PACF) functions.[209] The Durbin-Watson statistics was used to test for serial autocorrelation of the error terms in a regression model, with values close to 2.00 in the statistical output suggesting no serious autocorrelation.[209, 215] Where there is no/limited autocorrelation, residual versus time plots should show randomly scattered residuals and no particular pattern over time i.e. no serially correlated data, visual analysis of the residuals in this way also provides a method for checking the assumption of linearity.[209, 218] Deviations from this would indicate the model requires further adjustment and that long-term patterns haven't adequately been controlled for. The ACF and PACF statistical measures reflect how the observations in a time series are related to each other.[217] The ACF and PACF tests also assisted in determining the temporal structure of the series, i.e. the order of AR (p) and MA (q) parameters.

Once the order of the AR and MA parameters were estimated and tested, a final generalised least squares (GLS) segmented regression model was determined. The GLS models relied on population-level rates being conditionally normally distributed, which is relatively realistic particularly for studies with large sample sizes. To assess the fit of the GLS model parameters selected and finalise the model, the maximum likelihood ratio test (LHR) and quantile-quantile plots were used.[215] The likelihood ratio test was used to identify statistically significant better fit models (p values <0.05). The Akaike Information Criterion (AIC) output, which is a relative measure of model parsimony, produced from the LHR test was used to test the model quality and select the model with the fewest parameters that fits the data best.[215] A lower AIC value indicates a more parsimonious model, relative to the fit of the

comparison alternative model of the data being tested. According to TSA principles, a model with smaller numbers of parameters is preferential so as to provide a better representation of the underlying time series data, i.e. the simplest model is preferential and maintains a more accurate depiction of the properties of the time series, with a lower risk of over fitting the model. Once confident in the GLS parameters fit following the LHR test and qq-plot tests, the final ITS plot was produced and model coefficients extracted. These values where then used to predict the absolute and relative effects of the QP.

3.7.3 Sensitivity and subgroup analyses

ITSA frequently uses aggregate outcome data at the population-level. The aggregation of data assumes a uniform trend within the entire study population and that there are no individuals/groups within the population which may produce a different trend or effect to the overall population-aggregated trend. Assessment of the effects of an intervention on the total study population trends alone may mask certain effects which may be seen only in certain subgroups of the population. Conversely, the overall effects observed in the entire study population may be largely attributable to effects seen only in a particular group(s), i.e. differential effects of the intervention on the outcome for certain groups within the population. Subgroup analyses were undertaken for the ITSAs, where appropriate, creating more sophisticated ITS models to separate the potential effect modification (the differential effects of the intervention on the outcome due to a third variable) of different groups within the population. The influence of age as an effect modifier was assessed throughout the analyses by modelling separate ITSA models by age categories that span: children (1-15 years old), adults (16 – 64 years old) and the elderly (65 years and over). It was assumed that trends in RTI consultations, prescribing and complications would differ by age and this would not be evident if an overall population trend was solely assessed.

Similarly, several sensitivity analyses were completed to test different assumptions, for example whether using a different denominator (such as RTI episodes), would alter the trends and the impact of the intervention differently. Furthermore, a lag period was assessed, to attempt to identify whether there was a delay in the introduction of the QP and hence the potential full impact of the intervention. Where the same effect is detected under these different sensitivity tests and assumptions, this increases confidence in the inferences made.

3.8 Modelling impact of the QP, using hierarchical multivariable logistic regression

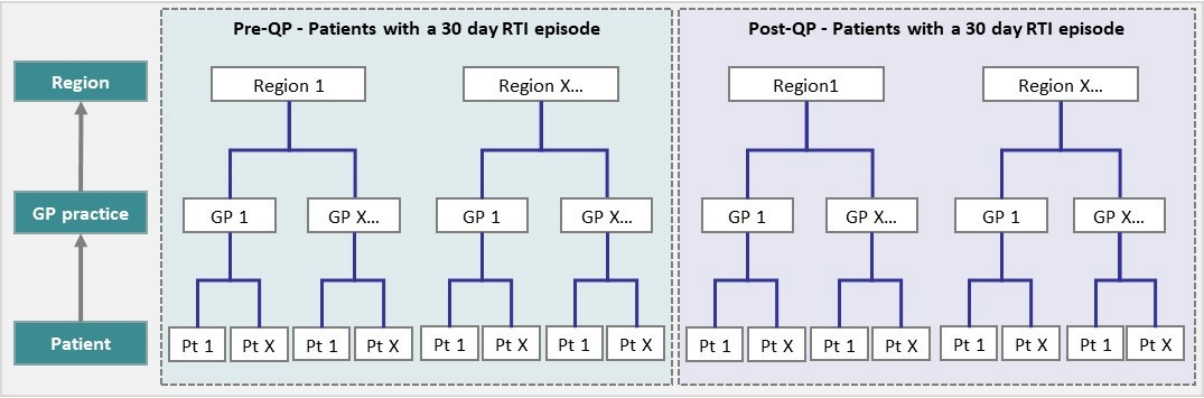
Hierarchical logistic modelling was used in Chapter 6 to either confirm and support findings from the chapters preceding it, or to propose different findings.

Logistic analysis is the analysis often used for binary outcomes, such as the development of complications which was the outcome of interest in Chapter 6. Multiple, or multivariable, regression is a technique used to test the association between the outcome of interest and numerous (or more than one) explanatory or predictor variables. Multilevel modelling (also known as hierarchical, or random effects modelling) goes further in that it is designed to take into consideration multiple structures or populations within the data, classifying these into clusters, and producing associations on the probability of the outcome based on each cluster having its own random effect.[222]

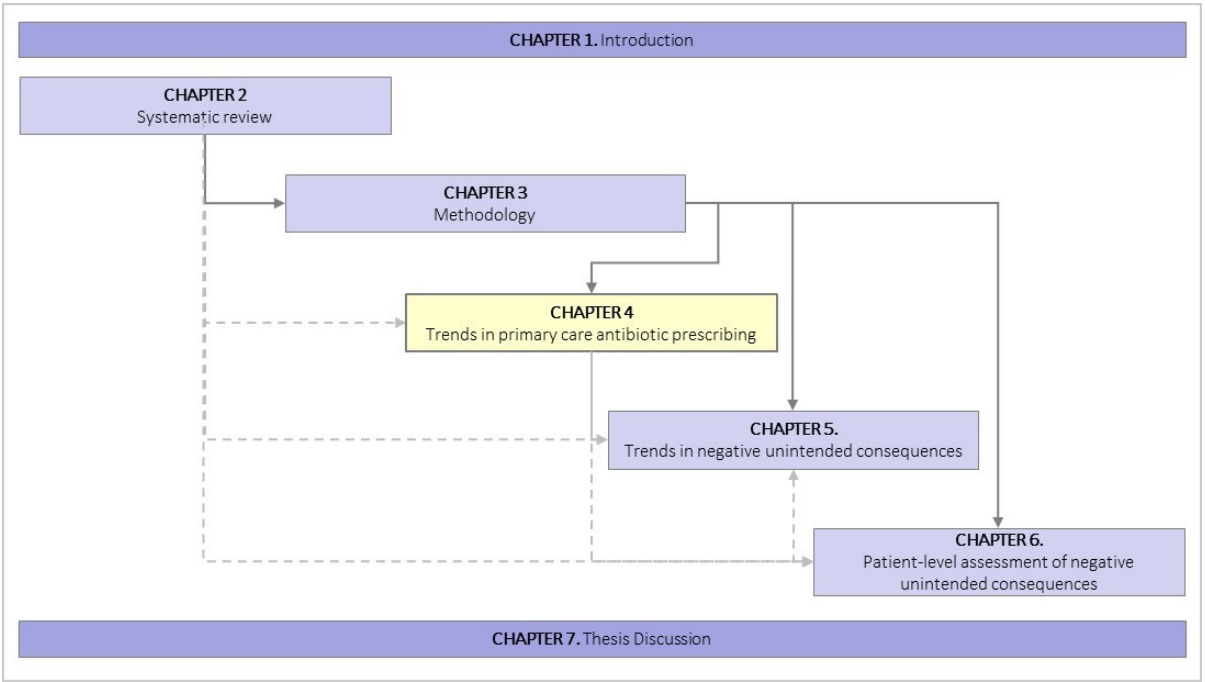
Multilevel data occur frequently, with observational data being inherently hierarchical, for example within the data assessed in this thesis patients are nested within healthcare providers (general practices), which themselves are nested within geographical areas. The notion behind clustering or grouping of data into classifications is that randomly selected individuals or patients from the same group or cluster are often more similar (in characteristics, health risks etc) than two other individuals selected randomly from outside the cluster. In this research (Chapter 6), the hierarchical models used two random-effects components to model intracluster correlation (observations in the same cluster as they may share similar random effects). The first random intercept was at the general practice level

and the second random intercept was at the regional level (Figure 3-6). It was thought that the same GP practice may tend to be more alike in exposure (e.g. how the QP is implemented, similar clinical decision making and antibiotic prescribing behaviours) as well as confounding or interactions (e.g. perhaps certain GP catchments/areas comprise predominantly older patients, who have greater comorbidities, or live in areas of higher AMR and are therefore prone to developing bacterial infections that are more difficult to treat). Similarly, clustering at regional level, accounts for any regional and local level similarities in AMR and AMS guidance and strategies, implementation of national interventions, and local area service provision. Multilevel regression models are a statistical technique used to produce estimates which account for these different levels of data and between- and within-cluster variation. The inferences produced from these models no longer treat the outcome as an independent observation but recognises structure to the data and produces estimates (regression coefficients, standard errors and significance tests) which may otherwise have been overestimated.

Figure 3-6. Depiction of multilevel classification and units



CHAPTER 4



Summary:

This chapter aimed to investigate the effect of the introduction of the 2015/16 QP on the trend of primary care antibiotic prescribing for RTIs, in England. ITSA were used to assess the antibiotic prescribing trend over a 6-year study period, adjusting for seasonality. The findings insinuate that the QP had its intended impact of reducing the rate of antibiotic prescribing, with a significant decline in the level of antibiotics prescribed for RTIs coinciding with the implementation of the QP, and a 3% relative decline 12-months post-QP. The greatest reductions in antibiotic prescribing were seen in younger patients. Reductions in broad-spectrum antibiotic prescribing were also noted.

Parts of the analyses completed in this chapter have been peer-reviewed and published in the Journal of Antimicrobial Chemotherapy (Appendix 39).[33]

4 TRENDS IN PRIMARY CARE ANTIBIOTIC PRESCRIBING

4.1 Introduction to investigating the trend in antibiotic prescribing for uncomplicated respiratory tract infections

Evidence suggests that primary care antibiotic prescribing acts as a key driver of antibiotic resistance.[26, 46] This is due to the high prevalence of antibiotic prescribing in this setting, particularly for patients consulting with uncomplicated RTIs (60%).[179] RTIs (including AOM, the common cold, sore throats, cough, acute bronchitis and sinusitis) are predominantly uncomplicated self-limiting infections, many of which are thought to be of viral aetiology.[223] Hence, antibiotic treatment for these infections is often considered as inappropriate as it is unlikely to confer clinical benefit to patients, whilst increasing the risk of adverse side effects such as toxicity, risk of *Clostridium difficile* infection, and the carriage of antibiotic-resistant bacteria (particularly with the inappropriate use of broad-spectrum antibiotics).[46, 175, 224] However, as was suggested in Chapter 2, early initiation of adequate antibiotic treatment has been associated with modest improvement in symptom severity and duration, as well as improved clinical outcomes for bacterial RTIs by preventing bacterial complications and propagation of infection, albeit that these outcomes are uncommon.[159]

A considerable number of antibiotic stewardship, educational, administrative and policy interventions have been simultaneously implemented in England, advocating judicious use of antibiotics, improvements in the appropriateness of prescribing, infection control, stewardship and increasing antimicrobial innovation.[5, 54] In England, one such implemented initiative introduced in April 2015 was the inclusion of an antibiotic prescribing element to the national Quality Premium (QP) 2015/16.[64] As discussed in Chapter 1, the QP financial incentives targeted, amongst other priorities, a reduction of antibiotic prescribing in primary care (by 1% of total antibiotics, and 10% of broad-spectrum antibiotics; specifically co-amoxiclav, cephalosporins and quinolones).[65, 66]

There is little evidence to date assessing the impact of the QP on antibiotic prescribing, particularly by indication. This chapter examines the potential impact of the QP on antibiotic prescribing in England, evaluating whether this was sustained post intervention, using an interrupted time series design, which is often used in the evaluation of 'natural experiments'.[211] The study extends over a 6 year period, 4 years pre-QP and 2 years post-QP, and includes patients who consulted for a RTI, as it is assumed that the greatest reduction in prescribing would be seen for patients with an RTI as they are the most common reason for presentation.

Several of the analyses completed in this chapter have since been peer-reviewed and published in the Journal of Antimicrobial Chemotherapy.[33]

4.1.1 Hypothesis

The hypothesis of the interrupted time series analyses is that the trend in antibiotic prescribing in England for RTIs after the introduction of the QP will have a different slope or level from those before the introduction of the QP. The null hypothesis is that there will not be a change in the slope or level of antibiotic prescribing post-introduction of the QP.

The aim of this study is to investigate the effect of the introduction of the QP 2015/16 on the trend of primary care antibiotic prescribing in the CPRD GP sample. Specifically, to:

a) Investigate whether there has been a shift/decrease in antibiotic prescribing for RTIs pre- and post-QP and to quantify any reductions seen in primary care.
b) Assess whether there has been a change in the proportion or trend in broad-spectrum antibiotic prescriptions.

Particular focus has been applied to age group stratification, as it is hypothesised that the young who consult more so than other older aged patients will be affected more so by any changes in antibiotic prescribing behaviours.

4.2 Method

4.2.1 Data sources and study population

The data sources and study populations have been defined in detail in Chapter 3. This retrospective study was conducted using data extracted from the CPRD database by identifying all patients who had an RTI consultation. Acute uncomplicated RTIs were classified as: AOM, rhinosinusitis, sore throats, upper RTIs, lower RTIs, viral RTIs, and total respiratory infections (total of all diagnostic codes excluding duplicated codes). Selection of the infections assessed and the related Read codes was inclusive, including symptoms and infections likely to be of viral aetiology. Diagnostic codes were excluded if they were not sufficiently specific to the infections of interest or were indicative of a more complicated infection, where antibiotic prescribing would be recommended. Full details of the Read codes used are available in Appendix 18.

The cohort of patients with an RTI were then analysed to see whether their consultation resulted in an antibiotic prescription. A prescription was linked to a patient's consultation if both occurred on the same day. The antibiotic therapy codes were identified and categorised by their British National Formulary (BNF) subchapter, with the exception of anti-tuberculosis and anti-leprotic drugs.[225]

A patient's data was eligible for inclusion if the patient had a Read code for an RTI between April 2011 and March 2017. Patients were included if they had permanent registration status (i.e. excluded temporary residents, visitors) from general practices who met a CPRD "up-to-standard" criteria, this ensured that the included data had been validated to meet reliable data quality levels for data completeness and recording (Chapter 3). Patients contributed data throughout the study period or

until the date of transfer of a patient to another general practice, date of death or the date at which the practice had its last collection.

4.2.2 Primary outcomes

Published research suggest that it is difficult to discern where a decrease in antibiotic prescribing has occurred whether this decrease was related to an impact of national campaigns targeting reductions in unnecessary antibiotic prescribing, or whether prescribing changes were associated to a decline in the incidence of disease, with rates of acute RTIs reported by UK general practices having declined by 45% between 1994 and 2000.[46] Monthly antibiotic prescribing rates per 1000 RTI consultations for all practices were estimated. The RTI consultation denominator was stratified by age where age-specific rates were being assessed. By using the RTI consultations as the denominator for the primary outcome, the rate calculation would take into consideration fluctuations or changes in the trend of consultations for RTIs over the seven-year time period. Hence, reductions observed in the prescriptions would not be due to reductions in RTI consultations, but more likely due to changes in general practitioner antibiotic prescription behaviours.

Rates were also analysed in terms of total antibiotic and broad-spectrum antibiotic prescribing. Aligned with the QP, broad-spectrum penicillins (which includes co-amoxiclav), cephalosporins and quinolones were the antibiotic BNF classes used to define board-spectrum antibiotics.

4.2.3 Statistical analysis: Segmented regression and adjustments for seasonality

As mentioned in Chapter 3, segmented regression analysis of ITS was used to estimate changes in the level and slope between the pre- and post-intervention time series, one year and two years following the introduction of the QP.

The data were firstly plotted to identify whether the general trend seen was reliable; to identify any outliers/wild points and to use the descriptive analysis for adjusting to the optimal model. A monthly time series of the rate of antibiotic prescribing from April 2011 to March 2015 was then used to establish the underlying trend, which was 'interrupted' by the intervention of interest, the QP.

Antibiotic prescribing for RTIs is known to demonstrate cyclic seasonal/monthly fluctuations. To model long-term seasonal patterns, the data were time stratified by months,[213] which permitted the adjustment of confounding by seasonality. To account for autocorrelated data, an Autoregressive Moving average (ARMA) model using the monthly-stratified segmented regression of antibiotic prescribing was fitted.[214] The order of the moving average (MA) and the autoregressive (AR) model parameters were determined using multiple methods: scatter plots of the deviance residuals versus time, the Durbin Watson test, the autocorrelation (ACF) and partial autocorrelation (PACF) functions. To assess the fit of the model parameters the maximum likelihood ratio (LHR) test and quantile-quantile plots (QQ plots) were used. Further details of these methods are available in Chapter 3.

Estimates of the pre-QP trend, the change in the trend post-QP and the change in the level immediately after the implementation of the QP were the model outputs investigated for statistical evidence as to whether there was a decrease in antibiotic prescribing at the time interval at which the QP was introduced. The model estimates were then used to quantify the absolute and relative changes at 12 months and 24 months.

STATA version 14 (STATA Corp, College Station, TX, USA) was used to perform the data management. The modelling and statistical tests were implemented in R Studio (http://www.r-project.org).

4.2.4 Sub-group analyses

Rates and trends were compared by age group and infection group. To assess potential differences in antibiotic prescribing by age, the data were split into three age groups: children (under 16 years old), adults (16 to 64-year olds) and the elderly (65 years and older). A further sensitivity assessment was carried out for patients under 4 years of age. The RTI Read codes were split into their categories of: AOM, rhinosinusitis, sore throat, upper RTI, lower RTI and viral respiratory infections, to assess whether reductions in antibiotic prescriptions were largely associated with particular diagnostic RTI groups.

4.2.5 Sensitivity analyses

The QP is an incentivised initiative targeted at the CCG-level and not the general practice level. Therefore, the time taken to implement the QP by disseminating information or developing local agreements could vary between CCGs and general practices and would not necessarily happen instantaneously. To account for such delay, a separate ITS regression model was developed with a 3-month phase-in period. This sensitivity analysis assessed the extent to which the results were influenced by a lag in the implementation of the intervention.

A further outcome measure using a different denominator was undertaken to ascertain whether any decreases seen were valid. The numbers of antibiotic items prescribed were expressed as a rate per 1000 registered patient and ITSA using this calculation were also undertaken.

4.3 Results

4.3.1 Descriptive analysis/ Trends in antibiotic prescribing over the study period

The study consisted of 2,198,602 registered patients who qualified as permanent patients and had consulted for an uncomplicated RTI (6,480,800 consultations) between April 2011 to March 2017. These patients attended and were recruited from 431 “up to standard” general practices in England (out of 643 UK wide practices eligible for inclusion).

At the individual patient-level, there was a near equal split between males and females included in the extract (Females: 1,228,585 [55.9%]). The mean age of patients was 37.15 years (SD: 25.7, age range 0-113 years).

Consultation rates for RTIs of registered patients over the six-year study period decreased by 28% from 2011/12 (342.8 per 1,000 registered patients) to 2016/17 (247.2 per 1,000 registered patients). The concurrent rate of registered patients prescribed antibiotics for RTIs also decreased over the years (36% decrease, from 173.32 to 110.12 per 1,000 registered patients) (Table 4-1 [Chapter 3 Figure 3.5]). Total antibiotic prescribing (per 1,000 RTI consultation) for all RTIs showed a decreasing trend across the study period (Table 4-1, [Chapter 3 Figure 3-5]) and seasonal fluctuation (Figure 4-1), with higher rates during the winter months (December) and lower rates in summer (August).

Table 4-1. Study population and summary of calculated rates by financial year, April 2011 to March 2017

		2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients		4,235,620	4,100,117	3,895,895	3,439,041	2,832,256	1,949,629
Patients who consulted with an RTI included in study		871,406	906,658	750,018	662,462	454,962	309,724
RTI consultations		1,451,984	1,522,399	1,231,712	1,080,171	712,590	481,944
Number of items of antibiotic prescription for RTI		734,137	763,329	602,620	517,236	322,185	214,695
RTI consultation rate, per 1000 registered patients		342.80	371.31	316.16	314.09	251.60	247.20
RTI prescription rate, per 1000 registered patients		173.32	186.17	154.68	150.40	113.76	110.12
RTI prescription rate, per 1000 RTI consultation		505.61	501.40	489.25	478.85	452.13	445.48
Broad-spectrum antibiotic prescription rate, per 1000 RTI consultations		312.93	307.49	295.05	290.29	268.78	267.44
Broad-spectrum antibiotics as a proportion of the total antibiotics prescribed for RTI, %		69.46%	69.33%	69.22%	69.80%	69.15%	69.89%
Rate of antibiotic prescribing per 1000 RTI consultations, with different recorded diagnoses	Acute Otitis Media	67.56	63.98	64.86	62.17	61.30	60.96
	Rhinosinusitis	719.30	705.28	687.31	676.99	648.10	641.49
	Sore throat	435.79	434.56	415.28	403.85	374.51	363.78
	Upper RTI	454.22	448.98	442.71	429.79	407.84	404.86
	Lower RTI	801.20	803.85	791.61	795.11	768.84	770.48
	Viral respiratory infection	122.95	126.47	105.18	101.23	82.93	84.81

The most commonly reported codes for a consultation were for upper RTIs, with 54% of consultations referring to such an infection. Assessment of the diagnoses groups further revealed that antibiotic prescribing was greatest for patients who had consulted with symptoms and diagnoses of Upper RTI (accounting for 48% of antibiotic prescriptions across the study period), followed by Lower RTIs (22%), AOM (13%), sore throat (9%), rhinosinusitis (8%) and lastly viral infections (1%; which should in theory not be prescribed antibiotics) (Appendix 25). The rate of antibiotics prescribing based on how often these diagnosis groups were consulted for reflected a different perspective, with lower RTIs and rhinosinusitis being the diagnosis groups most commonly prescribed antibiotics (770.48 and 641.49 per 1,000 RTI consultations in 2016/17 respectively,

Table 4-1, Appendix 25).

Of the age groups studied, children consulted more often than the other age groups for RTIs (418.11 per 1000 registered patient in 2016/2017 compared with adults 187.48 and elderly 277.08) (Table 4-2). Based on registered patients within a general practice, adults (16 – 64 years old) were prescribed the least antibiotics (89.2 per 1,000 registered patients in 2016/17) compared to children and the elderly (146.9 and 145.1 per 1,000 registered patients respectively). However, as adults also consult the least frequently (Table 4-2), the prescription rate per 1,000 consultations was relatively high (475.7 in 2016/17), with the elderly accounting for the highest rate of prescribing per consultation (523.7 per 1,000 RTI consultations). As mentioned, children, who consult the most often, have a lower prescribing rate per 1,000 consultations (351.3) (Table 1, Figure 3).

Table 4-2. Age group split of study population and calculated rates, April 2011 to March 2017

		2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients	Children	787,822	765,078	727,498	638,421	529,180	369,181
	Adult	2,746,673	2,642,003	2,501,145	2,196,580	1,801,340	1,231,297
	Elderly	701,125	693,036	667,252	604,040	501,736	349,151
RTI consultations	Children	473,076	497,250	399,414	349,093	229,696	154,360
	Adult	698,372	734,356	584,377	513,373	338,489	230,840
	Elderly	280,536	290,793	247,921	217,705	144,405	96,744
Number of items of antibiotic prescription for RTI	Children	191,184	202,431	156,572	134,904	82,204	54,230
	Adult	381,535	396,391	309,167	264,184	164,665	109,801
	Elderly	161,418	164,507	136,881	118,148	75,316	50,664
RTI consultation rate, per 1,000 registered patients	Children	600.49	649.93	549.02	546.81	434.06	418.11
	Adult	254.26	277.95	233.64	233.71	187.91	187.48
	Elderly	400.12	419.59	371.56	360.41	287.81	277.08
RTI prescription rate, per 1,000 registered patients	Children	242.67	264.59	215.22	211.31	155.34	146.89
	Adult	138.91	150.03	123.61	120.27	91.41	89.18
	Elderly	230.23	237.37	205.14	195.60	150.11	145.11
RTI prescription rate, per 1,000 RTI consultation	Children	404.13	407.10	392.00	386.44	357.88	351.32
	Adult	546.32	539.78	529.05	514.60	486.47	475.66
	Elderly	575.39	565.72	552.12	542.70	521.56	523.69
Broad-spectrum antibiotic prescription rate, per 1,000 RTI consultations	Children	278.08	278.54	266.37	263.74	239.68	238.25
	Adult	310.89	305.07	291.45	286.18	263.96	261.30
	Elderly	376.75	363.08	349.73	342.57	326.35	328.64

4.3.2 Segmented regression of ITS findings

The linear decrease in the antibiotic prescribing rate (prescription items per 1,000 RTI consultations) over the study period can be seen in Figure 4-1 (Appendix 26 provides the results of the underlying diagnostic tests and model build for this ITS). Although the antibiotic prescribing rate was decreasing prior to the introduction of the QP, by 0.83 prescription items per 1000 RTI consultations per month ($P < 0.0001$), there was a 3% drop in the rate (from an estimated counterfactual of 469.2 to 454.6 prescriptions per 1000 RTI consultations), corresponding to a reduction of 14.65 prescriptions per 1,000 RTI consultations ($P < 0.05$) that coincided with the implementation of the QP in April 2015. This reduction continued post-QP with no significant change in the slope of the trend (Table 4-3). Twelve and 24 months after the QP, the average monthly antibiotic prescribing rate was 14.6 per 1,000 RTI consultations less than would have been expected had the QP not been introduced. This represents a 3% decrease relative to that expected had the existing trend continued (Table 4-3).

Figure 4-1. A) ITS of total antibiotic prescription rate for RTI consultations in England, 2011/12 to 2016/17. B) ITS of total antibiotic prescription rate in England with a 3-month phase-in period

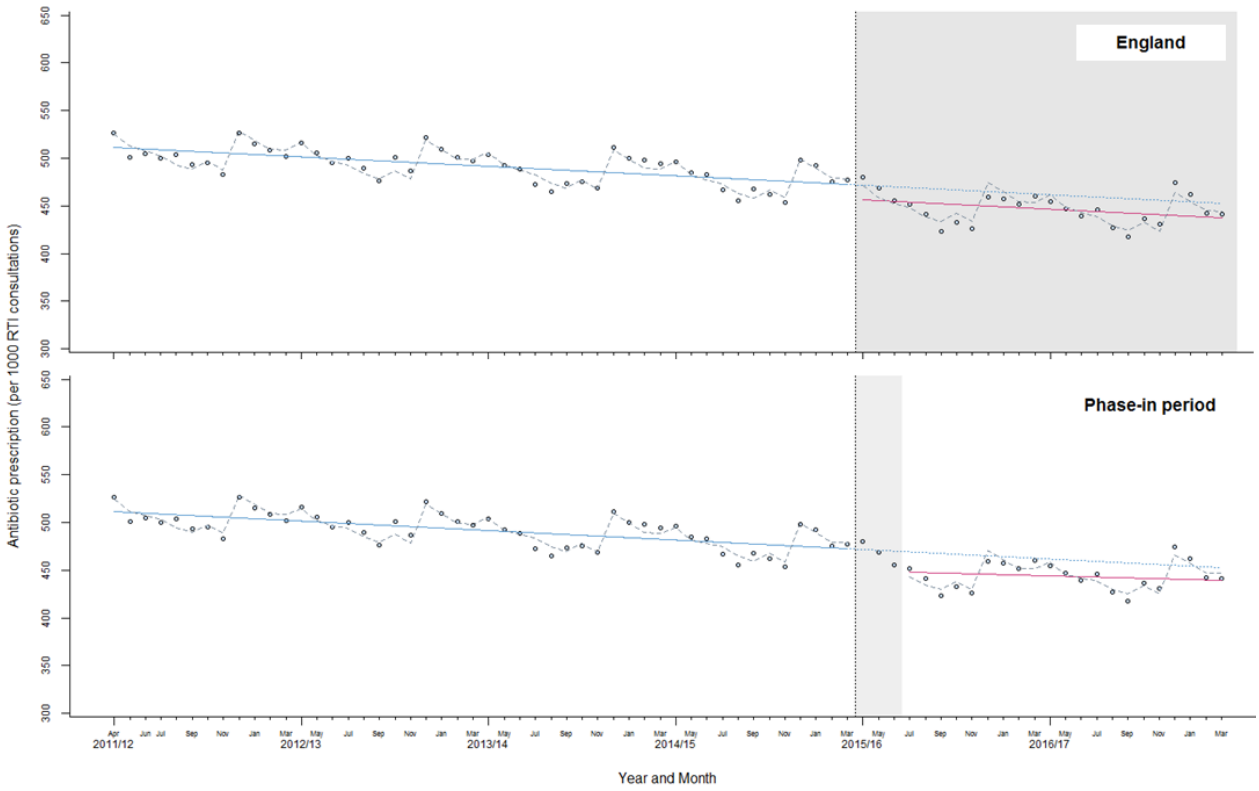
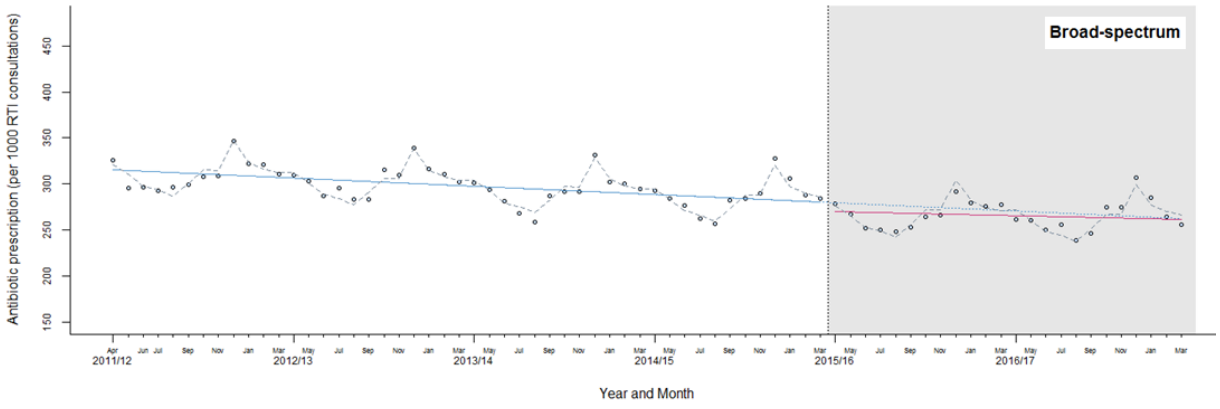


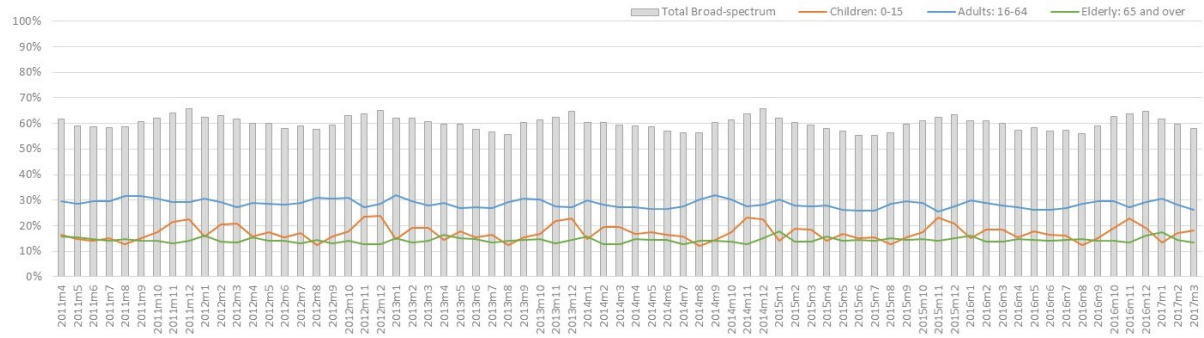
Table 4-3. Findings from the ITS analysis on the change in trend and level of antibiotic prescribing for RTIs and the relative and absolute changes post-QP

Prescribing measure, 2011/12 - 2016/17 (item/per 1000 RTI consultation)		Estimate of intercept	Pre-QP trend (*p*-value)	Change in level (*p*-value)	Change in post-QP trend (*p*-value)	Absolute change post 12 months	Relative change (%) post 12 months	Absolute change post 24 months	Relative change (%) post 24 months
England antibiotic prescribing		526.73 (<0.0001)	-0.83 (<0.0001)	-14.65 (0.0022)	0.0018 (0.9950)	-14.62	-3	-14.60	-3
Broad-spectrum antibiotic prescribing		321.18 (<0.0001)	-0.76 (<0.0001)	-8.53 (0.0022)	0.29 (0.0727)	-5.62	-2	-1.37	-0.5
Subgroup analyses:									
Age group	Children	418.85 (<0.0001)	-0.62 (0.0002)	-12.71 (0.0553)	-0.47 (0.3091)	-18.31	-5	-23.91	-6
	Adult	560.83 (<0.0001)	-0.91 (<0.0001)	-16.00 (0.0007)	0.17 (0.5315)	-18.03	-4	-20.05	-4
	Elderly	598.70 (<0.0001)	-1.02 (<0.0001)	-12.32 (0.002)	1.05 (<0.0001)	0.23	0	12.77	2
RTI group	Acute Otitis Media	65.80 (<0.0001)	-0.11 (0.0126)	-0.36 (0.8603)	-0.02 (0.8827)	0.58	1	0.81	1
	Rhinosinusitis	729.26 (<0.0001)	-0.62 (0.0002)	-12.71 (0.0553)	-0.47 (0.3091)	-6.36	-1	-5.91	-1
	Sore throat	462.08 (<0.0001)	-1.04 (<0.0001)	-13.75 (0.0869)	-0.07 (0.9028)	-14.54	-4	-15.33	-4
	Upper RTI	474.19 (<0.0001)	-0.76 (<0.0001)	-13.21 (0.0192)	0.28 (0.4297)	-9.88	-2	-6.55	-2
	Lower RTI	811.38 (<0.0001)	-0.23 (0.0461)	-24.11 (0.0002)	0.28 (0.4352)	-20.74	-3	-17.38	-2
	Viral respiratory infection	139.93 (<0.0001)	-0.70 (<0.0001)	-8.36 (0.2217)	0.39 (0.3565)	-3.72	-4	0.92	1
Sensitivity analysis:									
3-month phase-in period		525.08 (<0.0001)	-0.82 (<0.0001)	-21.39 (<0.0001)	0.44 (0.1186)	-19.86	-4.2	-14.53	-3.15
Age group: Children <5 years		381.30 (<0.0001)	-0.44 (0.0158)	-9.20 (0.2463)	-0.82 (0.1186)	-19.05	-5	-28.89	-8
Prescribing per 1,000 registered patients	England total	17.08 (<0.0001)	-0.07 (<0.0001)	-0.07 (0.9316)	-0.10 (0.0621)	-1.22	-7	-2.37	-15
	Children	21.78 (<0.0001)	-0.06 (0.1357)	-2.04 (0.2884)	-0.16 (0.1782)	-3.96	-15.0	-5.9	-22.90
	Adult	13.94 (<0.0001)	-0.06 (<0.0001)	0.00 (0.9990)	-0.07 (0.0653)	-0.80	-6.2	-1.60	-13.02
	Elderly	23.03 (<0.0001)	-0.07 (<0.0001)	-1.90 (0.0597)	0.04 (0.5564)	-1.48	-7.0	-1.06	-5.20

The most commonly prescribed antibiotic group was the broad-spectrum penicillins. The prescribing rate of broad-spectrum antibiotics decreased by 8.53 per 1,000 consultations per month (p<0.05). Whether this further reduction was sustained below what would have been projected without the QP is questionable as there was a positive change in the post-QP trend, although this reduction in the gradient of the post-QP slope was not statistically significant (Figure 4-1 A, Table 4-3). Notably of the antibiotics prescribed, the proportion of broad-spectrum prescriptions did not vary considerably between the years, a finding that was consistently seen in all the age groups (Figure 4-2 B, Table 4-3).

Figure 4-2. A) ITS of broad-spectrum antibiotic prescription rate for RTI consultations in England, 2011/12 to 2016/17. B) Proportion of broad-spectrum antibiotics prescribed, by age group

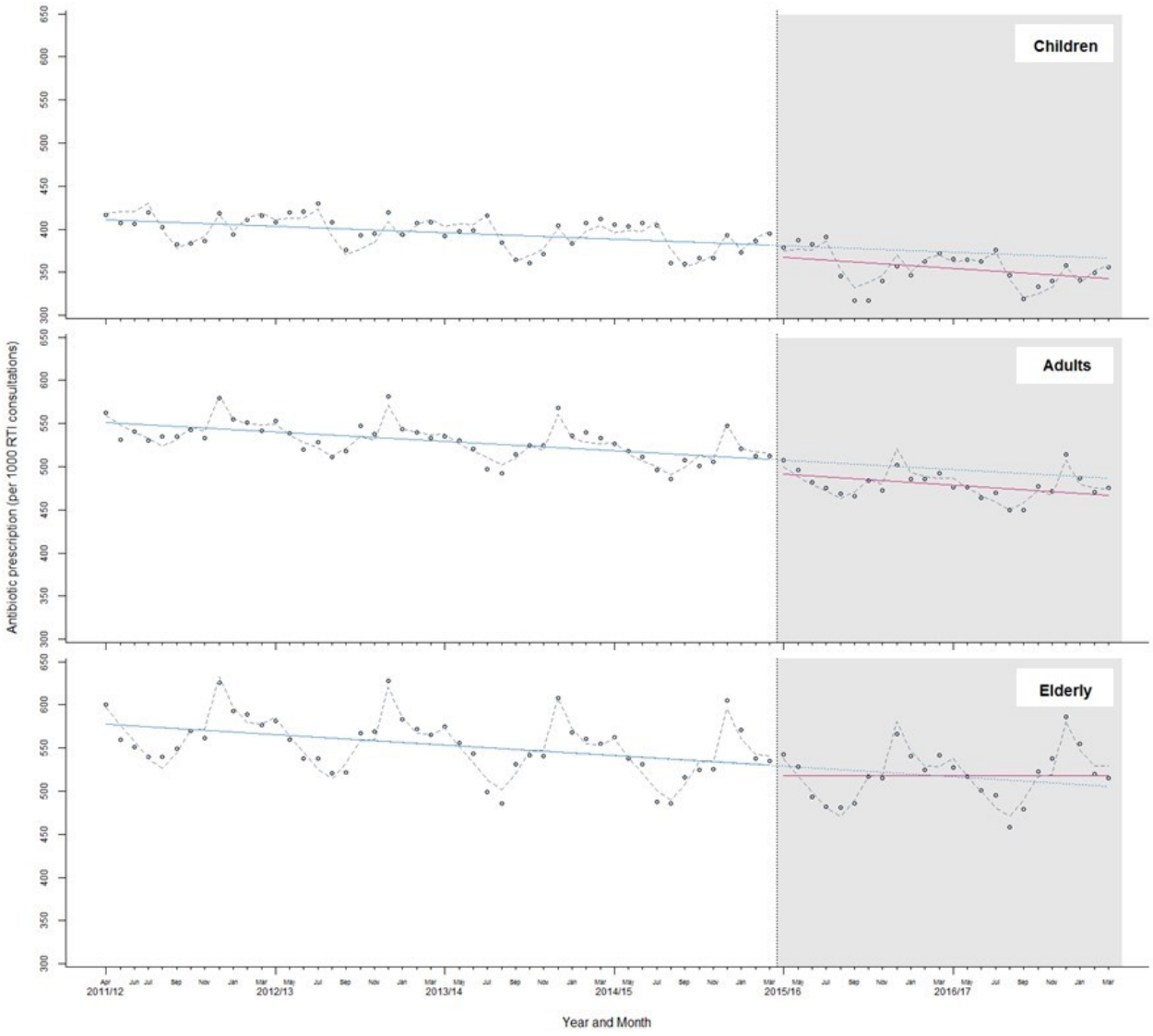




4.3.3 Sub-group analysis: Changes in antibiotic prescribing by age

The age-stratified ITS analysis illustrates that the impact of the QP differed across the three age groups, with the greatest absolute change reduction in antibiotic prescribing for RTIs occurring in children (Table 4-3). Two years post implementation of the QP, there was a 6% reduction in the children's rate of antibiotic prescriptions per 1,000 RTI consultations relative to what would have been expected had the pre-QP trend continued. At implementation of the QP, the change in level dropped across all the age groups, with the greatest decline seen in the adult category (decrease of 16 per 1,000 consultation, compared with 12.71 in children and 12.32 in the elderly) (Figure 4-3, Table 4-3). The ITS graphs illustrate that only the prescribing rate for children seemed to be widening from the counterfactual prescribing rate trend as time progressed, which was due to the change in the children's post-QP trend, which further declined by 0.47 per 1,000 consultations (children's post-QP trend was declining by 1.09 compared with 0.62 pre-QP, $p>0.05$).

Figure 4-3. Antibiotic prescription rate for RTI consultations in A) children, B) adults, and C) elderly, in England from April 2011 to March 2017.



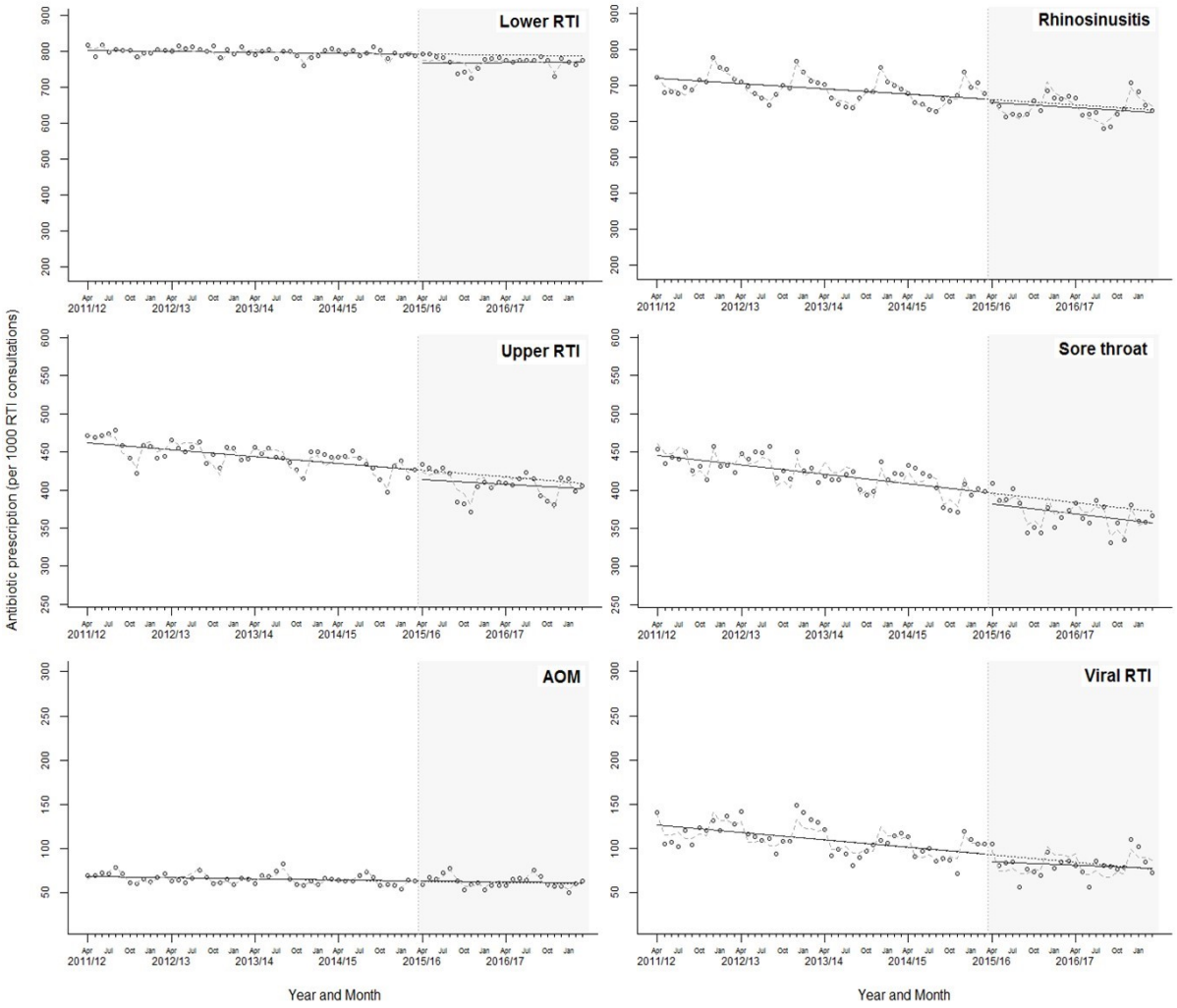
4.3.4 Sub-group analysis: Changes in antibiotic prescribing by RTI diagnostic group

Antibiotic prescribing for upper RTI consultations for adults and the elderly were higher than that seen for children (Appendix 27, higher trend lines over time in the elderly and adult age groups). However, prescribing for children showed the greatest decrease in absolute and relative change (Appendix 27 and Appendix 28), with the time series of the elderly category showing a shift post-QP to an increase in antibiotic prescribing compared to the pre-QP trend.

Consultations for lower RTIs and rhinosinusitis showed the highest rate of antibiotic prescribing, as indicated by the highest estimate of the intercepts in Table 4-3. Sore throats and lower RTI consultations showed the greatest decline in the level of antibiotic prescribing post-QP compared to the other infection groups (Table 4-3 and Figure 4-4), with a 4% and 3% decline, respectively, in antibiotic prescriptions per 1,000 consultations relative to the counterfactual expected rate at the same point in time. The majority of the reductions in the sore throat and the lower RTI groups were influenced by the decreases in the level and trend post-QP seen for children (Appendix 27 and Appendix 28).

The ITS for rhinosinusitis-related consultations showed an overarching decreasing antibiotic prescribing trend over time, although there were increased level and trend changes in antibiotic prescribing for children who had a rhinosinusitis consultation (increase of 16.61 in the level of antibiotics prescribed per 1,000 consultations in children, with a significant increase in the post trend of 1.47 per 1,000 consultations ($p<0.05$)).

Figure 4-4. Antibiotic prescription rate for RTI consultations stratified by infection group, April 2011 to March 2017



4.3.5 Sensitivity analysis: Time lag

Many interventions are implemented slowly, or effects may be delayed in their manifestation. In the instance of the QP it was thought that there may be a lag in the time to disseminate information through the healthcare hierarchy, i.e. a delay in the translation of a nation policy at CCG level to local agreements and an impact at general practice level and on GP behaviour. The change in antibiotic prescribing may therefore be delayed and a lag period of one quarter (3 months) was investigated. When the rates were censored around a 3-month implementation period, the change in the level was greater than had this lag not been included, and showed decrease in level of 21.39 per 1,000 consultations (*p<0.0001*) (Table 4-3). However, this level drop did not seem to be sustained, with the post-QP slope seeming to slightly level back towards the counterfactual line, i.e. the trend that would have been expected had the QP not been implemented (Figure 4-1). This was, however, not a significant change in the slope post-QP (Table 4-3). The reduction in the steepness of the slope post-QP was further demonstrated by the reduction in the decreasing relative change of 4.2 after 12 months to 3.15 after 24 months (Table 4-3).

4.3.6 Sensitivity analysis: Assessment of the very young and AOM by smaller age groups

Respiratory infections are common in immunologically naive children, and more so in pre-school children, with two thirds of children younger than four years old in the UK visiting general practices at least once a year with symptoms or diagnoses of a respiratory infection.[159] An ITSA was undertaken for children aged less than five years to identify whether the findings in children (<16 years) were influenced predominantly by prescribing changes in children aged less than five years. The TSA for children aged less than 5 years showed a level drop of 9.2 per 1,000 RTI consultations with implementation of the QP, and a greater slope decline of 0.82 per 1,000 RTI consultations. This resulted in a greater absolute change reduction in antibiotic prescribing for RTIs a year post-QP for children

aged less than 5 ears compared to a wider age category of under 16 years. However, the changes in level and slope in this age category were not statistically significant (Table 4-3).

Findings from assessment of infection groups showed that adults and the elderly had greater antibiotic prescribing rates in all infection groups apart from AOM, which was highest in children. When prescribing in children was analysed further for those with a diagnosis of AOM, prescribing was highest for children aged between 2-4 years old (Appendix 29). Reductions in the level and post-QP trend of antibiotic prescribing in children for AOM was most evident in children aged 5–15 years, however these were not statistically significant (Appendix 29).

4.3.7 Sensitivity analysis: Using the denominator of registered patients to assess changes in antibiotic prescribing by age

Analogous with the main analysis, the total antibiotic prescribing rate based on registered patients decreased slightly prior to the introduction of the QP, by 0.07 prescription items per 1000 registered patients per month (p<0.0001). With the introduction of the QP there was a level drop of 0.07 prescriptions per 1,000 registered patients (p>0.05) (Table 4-3, Appendix 30). There was a further decrease in the trend post-QP of 0.10 per 1,000 registered patients per month (p>0.05).

The elderly, who are prescribed more antibiotics than the other age groups, showed a statistically significant drop in the level of antibiotic prescribing (1.9 per 1,000 registered patients) coinciding with the introduction of the QP. Children demonstrated the greatest decline in both the level and trend in prescribing post-QP, however neither finding was statistically significant (Table 4-3, Appendix 30). Antibiotic prescribing in children also showed the greatest seasonality (peaks and troughs) throughout the years, with what appears to be an anomalous peak in prescribing in December 2014. A higher than expected level of prescribing was also seen for the elderly in December 2014 and January 2015 (Appendix 30).

4.4 Discussion

4.4.1 Summary of main findings

This chapter evaluated the impact of the QP 2015/16 on antibiotic prescribing for RTIs and on patient-level age-related prescribing, with certain age categories, particularly children, being affected more than others. The use of ITS analysis, a strong quasi-experimental design, allowed the control of pre-existing levels and trends to then detect any discontinuity in the ensuing post-QP level and trend. Following the introduction of the QP in April 2015, a decreasing trend in antibiotic prescribing for RTIs in primary care was observed, with seasonal peaks in the winter period and troughs in the summer. There was a significant drop in the level of this trend by 14.65 antibiotic items per 1,000 consultations in April 2015 ($p<0.05$), coinciding with the introduction of the QP. A year after the implementation of the QP there was a 3% relative reduction below the level of antibiotic prescribing for RTI consultations expected in the absence of this intervention. The findings suggest that this decline was sustained after two years. Additionally, there was a level drop in broad-spectrum antibiotic prescribing, although no differences were seen in the proportions of broad-spectrum antibiotics prescribed.

The rate of antibiotic prescribing across the study period, based on RTI consultations, was highest in adults for the majority of RTIs, and lowest in children, apart from AOM, an infection which is most commonly seen in the young. However, overall antibiotic prescribing for RTIs in children exhibited the greatest decline, with a 6% relative change in this age group two years post-QP. These reductions in prescribing for children were predominantly for upper RTIs, sore throat and lower RTIs (6%, 9% and 8% relative change 24 months post-QP, respectively). RTIs are most common in children, particularly those younger than 4 years (pre-school children). This is thought to be related to the immunological immaturity of young children which translates into an enhanced susceptibility to infection, with a concurrent greater tendency of subsequent health consequences, as well as longer duration of illness.[159] The pathophysiology of many infections and the clinical presentation of these infections

differ between children and adults for this reason. This along with parental uncertainty and anxiety regarding their child's infection may be responsible for the higher rates of consultations in this age group,[226] with research suggesting that two out of three children younger than four years visit their GP with an acute RTI at least once a year.[226] Doctors' concern around potential complications where a bacterial infection is not treated with antibiotics, difficulty in establishing a clinical diagnosis and perceived parental expectations may have contributed to high prescribing rates for RTIs in children.[33, 159] Along with growing GP and patient awareness of antibiotic stewardship, the introduction of the pneumococcal conjugate vaccine in recent years may have decreased the perceived risk of bacterial infections in children.[227] Adult and elderly patients who present less often at their general practice compared with children, often present with more pronounced or more numerous symptoms, are better able to communicate these subjective indications, and have greater underlying comorbidities.[33, 159] These factors may increase a GPs disposition to prescribe an antibiotic for adult and elderly patients. It would therefore be expected that the greatest reductions in antibiotic prescribing, as was seen in this research, would be made for children presenting with potentially self-limiting indications such as upper RTIs and sore throats. Assessment of the underlying lower RTI Read codes revealed that there were reductions in prescribing for bronchial cough, acute bronchitis and bronchiolitis, and acute tracheitis consultations. Decrease in prescribing for lower RTIs may be of potential concern, as antibiotics may be advisable in certain instances; these findings would benefit from further investigation and assessment of implications on subsequent complications, as reported in the succeeding chapter.

The ITSA that took account of a three-month phase-in period suggested that there were greater reductions in the level post-QP when a lag in the intervention was included. The QP was targeted at CCGs and therefore the time to disseminate information and develop local agreements would vary and would not necessarily have happened instantaneously. As mentioned in Chapter 1, there are various mechanisms by which an intervention implemented at CCG-level may have impacted on general practice-level prescribing behaviour, with suggestions that the use of Commissioning Support Units

(CSUs) and medicine management teams and pharmacists have had an important role in the dissemination of information and mediating local interventions.[70, 71]

The sensitivity analysis using registered patient as the denominator demonstrated a level drop coinciding with the introduction of the QP in April 2015 by 0.07 antibiotic items per 1,000 registered patients (Appendix 30). A year after the implementation of the QP there was a 7% relative reduction below the level of antibiotic prescribing for RTI consultations expected in the absence of this intervention, based on registered patients. Although visually a decrease can be seen in the trend, the findings from the sensitivity analysis were not statistically significant (Appendix 30). This sensitivity analysis also suggests that the previous winters influenza outbreak may have increased prescribing in December 2014, i.e. it can be visually seen that the winter before implementation of the QP there may have been a slightly inflated prescribing rate in December 2014 (there was a concurrent spike in RTI consultations in December 2014 [Chapter 3, Figure 3-5]).[228] However, utilising an ITS design takes into account fluctuations in seasonality and utilises more than one point in time to form a pre-intervention trend line, hence reducing the impact of effect modification or confounding caused by fluctuations in prescribing, although this cannot be ruled out as a source of elevation of the pre-QP prescribing slope.

4.4.2 Findings in relation to other published evidence

The reductions in antibiotic prescribing detected in this chapter reflect consultations for RTIs and not other indications, hence it is assumed that the total reductions in primary care would be more pronounced. A recent study assessing overall antibiotic items prescribed in primary care found an estimated relative decrease of 8.2% 24-months after the introduction of the QP (representing approximately 6 million fewer antibiotics prescribed during the 23-months post-QP).[92] This is in comparison to a 3% relative decrease in the rate per 1,000 RTI consultations (and a 15% relative decrease in the rate per 1,000 registered patients) 24-months post-QP found for RTI prescribing alone in this research.[33] The paper also reported that there was an 18.9% relative reduction in broad-

spectrum antibiotic items prescribed 24 months post-QP (with an estimated relative reduction of 10.1% broad-spectrum antibiotics prescribed as a proportion of total antibiotic items).[92] In contrast, this research found lower relative decreases of 2% and 0.5% of broad-spectrum antibiotic items (rate calculation per 1,000 RTI consultations) after 12 months and 24 months, respectively. The probable reason behind the variation between the broad-spectrum antibiotic findings in the study by Balinskaite *et al.* (2019) and the findings from this chapter is that, it is generally accepted practice that where bacterial RTIs carry a small risk of detrimental complications, based on clinical judgement, that they are treated with broad-spectrum antibiotics.[229, 230] Although narrow-spectrum antibiotics, such as Penicillin V, are often sufficient therapy.[79]

The findings are also corroborated by the 2018 ESPAUR Report, which documented significant and sustained declines in antibiotic prescribing of 13% (between 2013 and 2017, from 754 to 654 antibiotic prescriptions per 1,000 of the population, respectively).[231]

An assumption made when using ITS analysis is that the pre-intervention trend would have continued unchanged in the absence of the intervention of interest and that there are no competing interventions. In addition to the QP, other initiatives, guidance and reports have highlighted the importance of reducing inappropriate antibiotic prescribing (Chapter 1.3, Figure 1-2 and Appendix 1).[54] The retrospective nature of an ITS means that temporal associations can be described but causality cannot be inferred. It could therefore be problematic when attempting to discriminate between whether the changes seen were an artefact, truly an effect of the QP, or a cumulative impact of multiple initiatives. The QP is an NHS England-led national initiative, which provided a financial incentive for reductions in antibiotic prescribing in primary care, an approach which several studies have indicated as being effective in bringing about change in prescribing.[232-234] There are, however, studies reporting improvements occurring prior to the schemes and no discernible reductions in antibiotic prescribing.[235-239] In England, the positive influence of financial incentives on clinical outcomes has been previously shown with the Quality and Outcomes Framework in 2004 (Chapter

1.3.3),[234, 240] although positive effects were not universal[235] and there were associated concerns about unintended consequences.[238, 241] The results in this chapter do show that although a decreasing trend was evident prior to the QP, there was a statistically significant further decrease in antibiotic prescribing when compared to the expected counterfactual trend had the QP not been introduced. The study also accounted for variations in consultation rates by using RTI consultation counts as the primary denominator, which infers that the antibiotic prescribing reductions seen were not due to changes in the incidence of infections.

Previous UK studies, as well as studies in Sweden, The Netherlands, and the USA, have shown declining trends in both consultation rates and antibiotic prescribing for acute RTIs,[3, 77, 172, 242] and have suggested that where reductions in antibiotic prescribing arose, this was mainly because the rate of infections had been declining.[3, 172] The reduction in consultations seen was either due to a true decrease in the incidence and severity of RTIs (with perhaps recent reductions in the frequency of RTIs being accounted for by the increased protection provided from a wider range of immunisations against respiratory infections e.g. *streptococcus pneumoniae*),[3] or to the growth in public awareness around health issues, antibiotic consumption and self-management.[3, 242] The count of RTI consultations was used as the primary denominator for the rate calculations, attenuating for changes in consultations and therefore identifying changes to prescribing behaviours in primary care.

4.4.3 Strengths and limitations

A limitation of the data used is that collection of CPRD data is not primarily for research purposes, and as with all routine data, there is an inherent risk of miscoding and misclassification bias due to differences in the accuracy and completeness of clinical codes used by GPs and/or over time. However, the use of CPRD routine care data rather than audit-based data, lowers the possibility of intentional misclassification. Furthermore, to reduce selection bias and account for any shifts in coding, the selection of READ codes for RTIs was comprehensive, including symptom, diagnosis codes and viral

respiratory infections. Having studied a large number of patients and included practices with good quality data, the sample is believed to be representative of the population in England and generalisable to other countries with similar healthcare settings.[33, 243, 244]

There may have been an increased use of "deferred" or "delayed prescribing" in recent years, an identified mechanism to reduce antibiotic consumption, whereby patients being prescribed an antibiotic are advised to "delay" use to when illness duration is prolonged and symptoms persist. Furthermore, not all prescriptions issued may have resulted in antibiotics being dispensed, and of the antibiotics prescribed it was not possible to assess changes in the duration or dosage of antibiotic prescriptions due to limitations in the completeness of related data fields. However, national data have demonstrated that reductions in the number of antibiotic items prescribed has shown equivalent reductions in standardised volume of prescribing.[77] Additionally, CPRD practices voluntarily include themselves within the data collection scheme, and although patients have been shown to be representative of the population, the included practices may have different or better antibiotic prescribing behaviours, hence may not have exhibited the same reductions as that seen nationally, suggesting that the estimated findings may be an underestimation of the antibiotic decreases which may have occurred nationally.

This chapter provided detailed insight into consultation and antibiotic prescribing trends for RTIs over six years in a population of over 2 million registered patients. As antibiotics are not available over-the-counter in the UK, patients are prescribed antibiotics through a medical consultation, predominantly with general practitioners in primary care. The data assessed were therefore highly representative of antibiotic management in primary care. The focal strength and the novel aspect of the research completed in this chapter is that consultations and antibiotic prescribing have been linked to clinical diagnoses and symptoms, providing assessment of a national intervention on particular indications,

namely RTIs, which are the most common conditions consulted for and prescribed antibiotics in primary care.

4.4.4 Conclusions

In summary, the findings from this chapter demonstrate significant reductions in prescribing of antibiotics for RTIs following the implementation of the 2015-16 QP, with the greatest reductions seen in children. Many patients were still prescribed antibiotics for upper RTIs such as sinusitis, AOM and sore throats, which guidance suggests are likely to be self-limiting infections where antibiotics offer little clinical benefit. Further reductions in primary care antibiotic prescribing should therefore still be achievable. However, it will be important to monitor whether reductions in antibiotic prescribing are associated with any increases in morbidity and subsequent complications, such work to address this issue is reported in the next chapter.

4.4.5 Recommendations and implications for practice or research

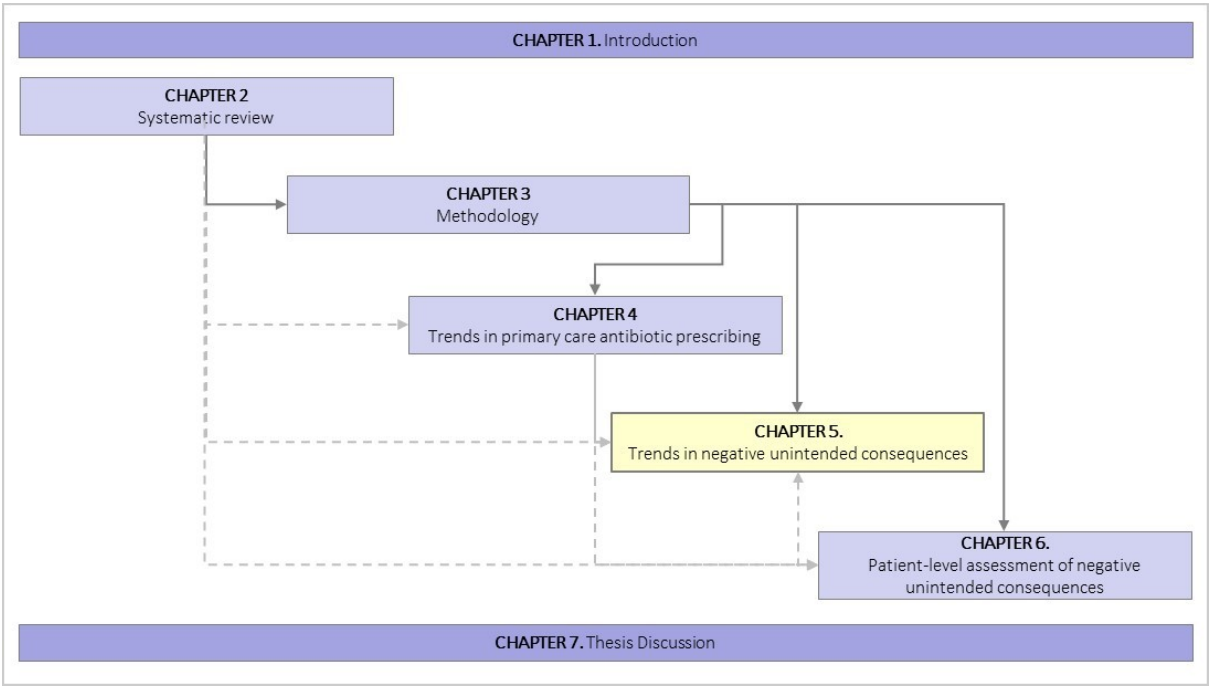
Further work is needed to investigate whether a similar reduction in antibiotic prescribing in primary care is seen for patients presenting with other infection indicators and whether this influences the rate of treatment failure, measured by the rate of re-consultation within the same episode of infection, or whether the opposite occurs with patients consulting less frequently.

TSA uses an approximation of a true counterfactual, in that it's not possible to observe a given intervention being implemented and not being implemented in the same population at the same time. Hence, the counterfactual used is an extension of the pre-existing trend and is estimated based on the assumption that the pre-existing trend line would continue in a similar manner had the intervention not occurred. The true counterfactual is therefore never known and inferring causality is problematic.

A comparison or control group may strengthen the findings and may inform on whether financial incentives are truly necessary as an impetus for change, i.e. utilising counterfactual inference.[206] A control group or population which shares similar characteristics where the intervention was not implemented would increase the finding's validity. Scotland, Wales and Northern Ireland would make useful comparison populations as these populations would be largely similar to the England intervention group but differ in that the QP was not implemented in these countries.

The findings suggest that a change in antibiotic prescribing behaviours occurred following the introduction of the QP. It seems likely that further reductions in prescribing could be made, as implied by the fact that certain conditions, which are thought to be predominantly self-limiting, as well as microbiologically undiagnosed viral infections, may still be inappropriately prescribed antibiotics. However, given the uncertainty around optimal treatment of infections, in terms of not knowing the aetiology of infections recognised on purely clinical grounds, it is imperative to identify whether reductions in prescribing have led to negative unintended consequences particularly increases in morbidity or mortality. This concern is addressed in the subsequent chapter.

CHAPTER 5



Summary:

This chapter utilised national routinely linked datasets, as described in Chapter 3, to investigate whether patients who had consulted with a RTI in primary care had correlated increases in re-consultations, complications, or had died, as an unintended consequence of the introduction of the QP (i.e. due to related reductions in antibiotic prescribing, as was seen in Chapter 4). The ecological associations between the introduction of the QP and adverse outcomes was explored using interrupted time series analyses, with no significant related impacts seen. However, increases in complications (e.g. pneumonia in primary care and bloodstream infections in secondary care [p>0.05]) were reported, in the elderly (≥65 years) and patients who had been prescribed antibiotics; increased mortality was also noted.

5 TRENDS IN UNINTENDED CONSEQUENCES

5.1 Investigating the trend in unintended consequences for uncomplicated RTIs

The previous chapter demonstrated that there was a significant reduction in antibiotic prescribing coinciding with the introduction of the QP 2015/16.[33] The QP was introduced with the aim of reducing unnecessary antibiotic use, in order to reduce the selective pressure for the emergence and spread of AMR. However, a reduction in antimicrobial prescribing at the population-level, aimed at ameliorating resistance rates, may result in instances of patients with RTIs of bacterial aetiology not receiving antibiotics, resulting in prolonged carriage of these respiratory pathogens.[177] This in turn could result in patients developing more severe infections, which would constitute an unintended consequence of the implementation of the QP. Just as previous increases in antibiotic prescribing resulted in bacterial resistance, there needs to be an awareness of the potential impact that reduced prescribing could have on the incidence of more severe bacterial infections, referred to hereafter as "complications". Hence a balance needs to be made between preserving the usefulness of antibiotics through prudent antibiotic prescribing and antimicrobial stewardship, and paralleling this with the awareness of the potential risks of reducing antibiotic prescribing, such as increased morbidity or mortality.[3]

The systematic literature review (Chapter 2) showed there is inadequate evidence to determine the extent, if any, that reductions in antibiotic prescribing are associated with unintended consequences. Recent published research found no significant association between the introduction of the QP and subsequent complications of infections, where complications were combined into one category.[91] The findings did, however, identify significant changes in hospital admission or GP consultation rates for certain conditions; namely an increase in hospital admissions for quinsy, but decreases in hospital admissions for scarlet fever and GP consultations for empyema and scarlet fever.[91] The research carried out in this chapter builds on these findings, by analysing data on patients who have consulted in general practices for uncomplicated RTIs and linking patient-level infection episodes to subsequent

GP re-consultations, hospital admissions and death, i.e. the analyses assessed outcomes following an RTI consultation and were not an assessment of general hospital admissions or primary care consultations. The literature describes an 'illness iceberg in general practice', in that for every five RTIs in the community, only one is thought to present to the general practice.[245] Where index uncomplicated RTIs develop into complications, which could have otherwise been prevented with the use of timely and appropriate antibiotic therapy, it is important that the outcomes assessed are in reference to such prodrome infections which were consulted for in primary care. Hence, it would be preferential to only include patients who had prior RTI consultations when associations are assessed between the introduction of the QP 2015/16 (observed reductions in antibiotic prescribing) and subsequent complications.

5.1.1 Hypothesis

The hypothesis for the studies in this chapter is that subsequent to the introduction of the QP there have been suboptimal reductions in antibiotic prescribing for predefined infections in the primary care setting, resulting in adverse unintended consequences, namely increased morbidity and mortality measured as an increase in primary care consultations, hospital admissions and death.

The aims of this chapter have been divided into four to identify possible adverse unintended impacts of the QP (depicted in Figure 5-1):

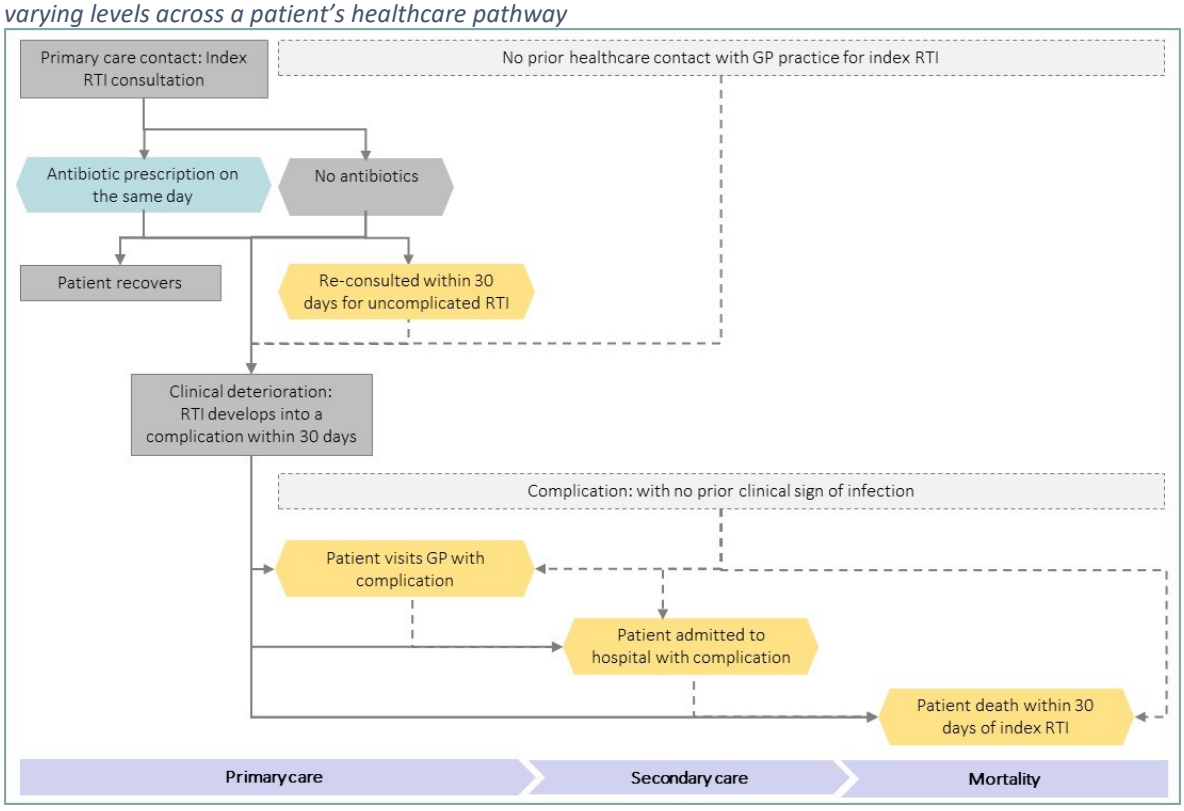
A. Re-consultations in primary care: Identify whether there has been subsequent increase in the use of health care services as measured by returning visits to general practices for persistent RTI symptoms and diagnoses following an initial consultation for RTI.

B. Complications in primary care: Identify whether there has been an increase in the occurrence of subsequent more severe infections consulted for in primary care, following an initial consultation for RTI.

C. Complications in secondary care: Identify whether there has been an increase in the occurrence of subsequent more severe infections in patients requiring hospital admission, following an index RTI consultation in primary care.

D. Complications as measured by mortality: An increase in death within 30 days of the index RTI consultation.

Figure 5-1. Respiratory tract infection to complication conceptual model, including how this is captured at varying levels across a patient's healthcare pathway

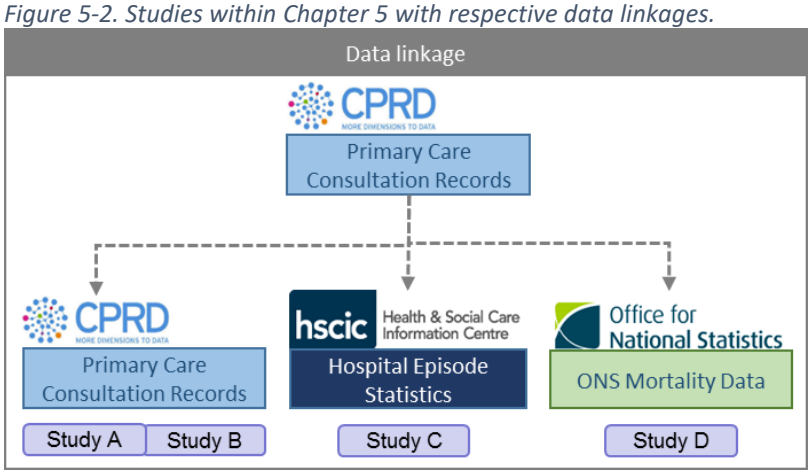


Note: Yellow boxes identify the outcomes which were assessed as part of the aims of this chapter. Dotted lines and boxes refer to information not captured in this research.

5.2 Method

5.2.1 Data sources and linkage

Figure 5-2. Studies within Chapter 5 with respective data linkages.



The study population included all CPRD "acceptable" patients with permanent registration status (i.e. excluded temporary residents and visitors), who had not 'opted out' from providing data in up-to-standard participating English general practices. This ensured that the data collected from practices had been validated to meet reliable quality of completeness and recording. Study participants were included if they had had an index visit at a general practice for an uncomplicated RTI within the study period of March 2011 to April 2017. Further details of the data sources used, data linkages and how the data were managed can be found in Chapter 3.

Study A and B: Using primary care consultation data

Patients who had consulted with an uncomplicated RTI identified in the CPRD database, were linked back to their primary care patient medical records using the CPRD consultation table to identify those patient consultations which resulted in:

A. Re-consultations for CPRD Read codes for uncomplicated RTIs (i.e. similar or the same uncomplicated RTI diagnoses and symptoms) within 30 days of the index RTI infection.

B. Consulted for CPRD Read codes of infectious complications related to the index RTI within 30 days (Figure 3-1, Chapter 3, exemplifies the pathway from an uncomplicated RTI to the outcomes assessed).

Following a rapid search of the published literature to identify the duration of infection episodes, as well as incorporating clinical input from a practicing GP, a 30 day follow-up duration was chosen as the most reliable in providing enough follow-up days to ensure outcomes related to the index infection were captured, but not too long a duration that any outcomes seen would be unrelated to the index RTI (further information in Chapter 3.4.3).

Study C: Using hospital admission data

As referred to in Chapter 3, HES data contain details of all patients admitted to NHS hospitals in England. HES was used to inform the clinical outcomes of any admissions into hospital and the occurrence of subsequent more severe infections in the hospital setting. Patients RTI consultation records were linked to HES admission records. The RTI patient CPRD data was too large for the routine CPRD linkage process, instead a list of ICD-10 codes were used alongside the CPRD IDs in order to obtain patients who had been admitted for the complications of interest between April 2011 to March 2017.

The HES data were linked to each patient's initial index CPRD RTI consultations if the hospital admission occurred within a 30-day follow-up. Complications were retained if the ICD-10 code for a complication was recorded within the first hospital episode of care within a spell (i.e. hospital admission). Complications were combined into one outcome variable and were recorded as binary (i.e. a patient experienced a complication or did not), as certain complications were too rare to assess alone, particularly when stratified by month, as was done for the ITS analysis. Multiple complications for the same patient were counted separately if the complications occurred in separate infection episodes and not within the same follow-up duration, i.e. was a separate complication for a different index

uncomplicated RTI. Patients and their index consultations were excluded from this study if the practice with which they were registered with was not eligible for HES linked data or they had opted out of data linkage, as no outcomes would be provided for these patients whether they had had a complication or not. Hospital admissions which occurred on the day of index primary care consultation were not included as outcomes, as it was deemed that these hospital admissions were not related to the prescribing decisions made in primary care on that day, or as effects of the QP.

Study D: Using ONS mortality data

Similarly to the HES linkage, Patient CPRD IDs were linked to the ONS mortality database. ONS mortality data contains the date and details of all deaths for the population in England (Chapter 3). The linked data extract included all patients who had consulted in primary care with an uncomplicated RTI index infection who had died at some point during the study period. Although all-cause mortality was the primary outcome of interest in this section, the ONS data provided mortality information pertaining to the reason of death (ICD-10 codes). The mortality outcomes were linked to the initial CPRD consultations to identify whether the deaths occurred within 30 days of the index infection. Only patients who were eligible for ONS linkage were included in this study section.

Complications were aggregated for patients with multiple ICD-10 codes and were assessed as an outcome variable which stated whether a patient had died within the 30-day follow-up period, or specifically had died with a code related to the complications of interest within 30-days. Deaths which occurred on the day of the index infection were not included as an outcome as the death was deemed unrelated to whether the QP was implemented or whether the patient received an antibiotic or not.

5.2.2 Primary outcomes

Re-consultations for uncomplicated RTIs were calculated as monthly rates per 1,000 registered patients. The complications assessed (in primary care, secondary care and mortality data) were calculated as monthly rates per 100,000 registered patients. Analysis using RTI episodes as the denominator was completed where appropriate (per 100,000 RTI episode). This would provide the rate of complications in patients who had RTIs and who would have been at direct risk of developing a complication, rather than assessing population risk.

Patients were recorded as not having had a study outcome event if nothing had been recorded or linked to by the end of the follow-up period (30 days) i.e. the patient was assumed to have recovered.

5.2.3 Statistical analysis: Segmented regression and adjustments for seasonality

As mentioned in Chapter 3, segmented regression ITS models were used to analyse the associated impact of the introduction of the QP 2015-16 on the occurrence of the unintended consequence outcomes of interest. Complications were aggregated by month over a 6-year period (April 2011 to March 2017).[209]

As with Chapter 4, the data were initially plotted to identify whether the general trend seen was reliable, to identify any outliers and to use the descriptive analysis in adjusting to the correct model. The final segmented regression models fit a least squares regression line to each segment. As well as antibiotic prescriptions, infections and related complications of RTIs are known to demonstrate cyclic seasonal fluctuations. To model long-term seasonal patterns, the data were time stratified by months.[213] To account for autocorrelated data, an Autoregressive Moving average (ARMA) model using monthly-stratified segmented regression was fitted.[214] The order of the moving average (MA) and the autoregressive (AR) model parameters were determined using scatter plots of the deviance residuals versus time, the Durbin Watson test, the autocorrelation (ACF) and partial autocorrelation (PACF)

functions. To assess the fit of the model parameters the maximum likelihood ratio (LHR) test and quantile-quantile plots (qq plots) were used. Further details are available in Chapter 3.

Estimates of the pre-QP trend, the change in the trend post-QP and the change in the level immediately after the implementation of the QP were the model outputs which provided statistical evidence as to whether there were unintended negative impacts which occurred at the time interval at which the QP was introduced. The model estimates were then used to quantify the absolute change and relative change at 12 and 24 months. All reported p-values were considered as two-tailed and significant if p-value <0.05.

5.2.4 Sub-group and sensitivity analyses

To assess whether the results seen were attenuated by antibiotic prescribing, data were stratified in terms of whether patients were or were not prescribed antibiotics at the index consultation.

To assess whether there was a difference in the occurrence of complications related to the introduction of the QP by age, the rates and trends throughout all the studies were assessed following stratification into three age groups: children (under 16 years old), adults (16 to 64 year olds) and the elderly (65 years and older).

Study A: Re-consultations in primary care

Alongside the rate of re-consultations, trends of re-consultations within 30 days as a proportion of the total index RTI consultations were also calculated and an ITS analysis completed.

Study B: Complications reported in primary care

CPRD complications: Of the outcomes assessed, mastoiditis, scarlet fever, quinsy, pneumonia, and BSIs/sepsis were assessed descriptively as separate outcomes and where appropriate by age category.

Although all the outcomes recorded were uncommon, rheumatic fever, glomerulonephritis, empyema, brain abscess and meningitis were extremely rare and were not assessed separately.

Study C: Complications reported in secondary care

Based on whether there were small numbers of infection episodes which resulted in a complication, only certain outcomes were assessed separately, these being pneumonia and BSIs.

As a sensitivity analysis, hospital admission trends were also assessed based on ICD-10 codes listed as the primary code for the episode only, i.e. not including codes listed within the first hospital episode or spell.

Study D: Mortality data

All-cause mortality was assessed alongside mortality related to complications of interest.

5.3 Results- Study A: Re-consultations for the same or similar uncomplicated RTIs

5.3.1 Trends in re-consultations over the study period

Between April 2011 and March 2017, a total of 2,198,602 patients (mean age: 37.15 [SD: 25.7], age range=0-113 years; females: n=1,228,585, 55.9%) who were registered at 431 general practices across England had 6,480,800 consultations for RTIs. Of these, 5,463,593 consultations were created as index RTI consultations, i.e. the remaining consultations occurred within 30 days of the index RTI diagnosis. Of the index initial RTI consultations, 856,203 (16%) resulted in a re-consultation within 30 days for similar uncomplicated RTI diagnoses. Re-consultation rates and proportions decreased over the 6-year study period by 33% and 8%, respectively from 2011/12 (45.91 per 1000 registered patients and 15.93% of the total index RTI consultations) to 2016/17 (30.98 per 1000 registered patients and 14.70% of the total index RTI consultations). The re-consultation trends (in rate and proportion) depicted evident seasonal cyclic peaks during the winter periods (Figure 5-3). Patients who were prescribed an antibiotic at the index consultation generally had higher proportions of re-consultations than those not prescribed antibiotics, although this finding exhibited seasonal variation with higher re-consultation rates in summer (particularly August) and lower in winter (December).

Of the age groups studied, the rate of re-consultations, based on registered patients, was consistently highest in children, although as a proportion of the total index RTI consultations, the elderly re-consulted most often within 30 days (Appendix 31). Of the underlying index RTI groups assessed, patients who had lower RTI indications re-consulted more often than the other groups (i.e. AOM, rhinosinusitis, sore throats, upper RTIs and viral respiratory infections).

Table 5-1. Re-consultations in primary care: Study population and summary of calculated proportions and rates by financial year, April 2011 to March 2017

Parameter	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients	4,235,620	4,100,117	3,895,895	3,439,041	2,832,256	1,949,629
Patients who consulted with an RTI included in study	871,406	906,658	750,018	662,462	454,962	309,724
Total RTI consultations	1,451,984	1,522,399	1,231,712	1,080,171	712,590	481,944
Index RTI consultations	1,220,507	1,277,152	1,040,012	908,961	606,199	410,762
Re-consultations within 30 days of index RTI consultation	194,438	205,853	161,370	144,077	90,074	60,391
Re-consultations within 30 days as a proportion of the total index RTI consultations, %	15.93	16.12	15.52	15.85	14.86	14.70
Re-consultations within 30 days, per 1,000 registered patients	45.91	50.21	41.42	41.89	31.80	30.98

5.3.2 Segmented regression of ITS findings

Slight reductions in the level and the trend of re-consultations occurred in all (apart from the trend in the elderly sub-group analysis) of the ITS models (Figure 5-3). However, there were no significant changes in the level post-QP of re-consultation rate, proportion, or by age group (P>0.05) (Table 5-2).

Figure 5-3. Interrupted time series analyses of the RTI re-consultation rate and proportion within 30-day follow-up in England, April 2011 to March 2017

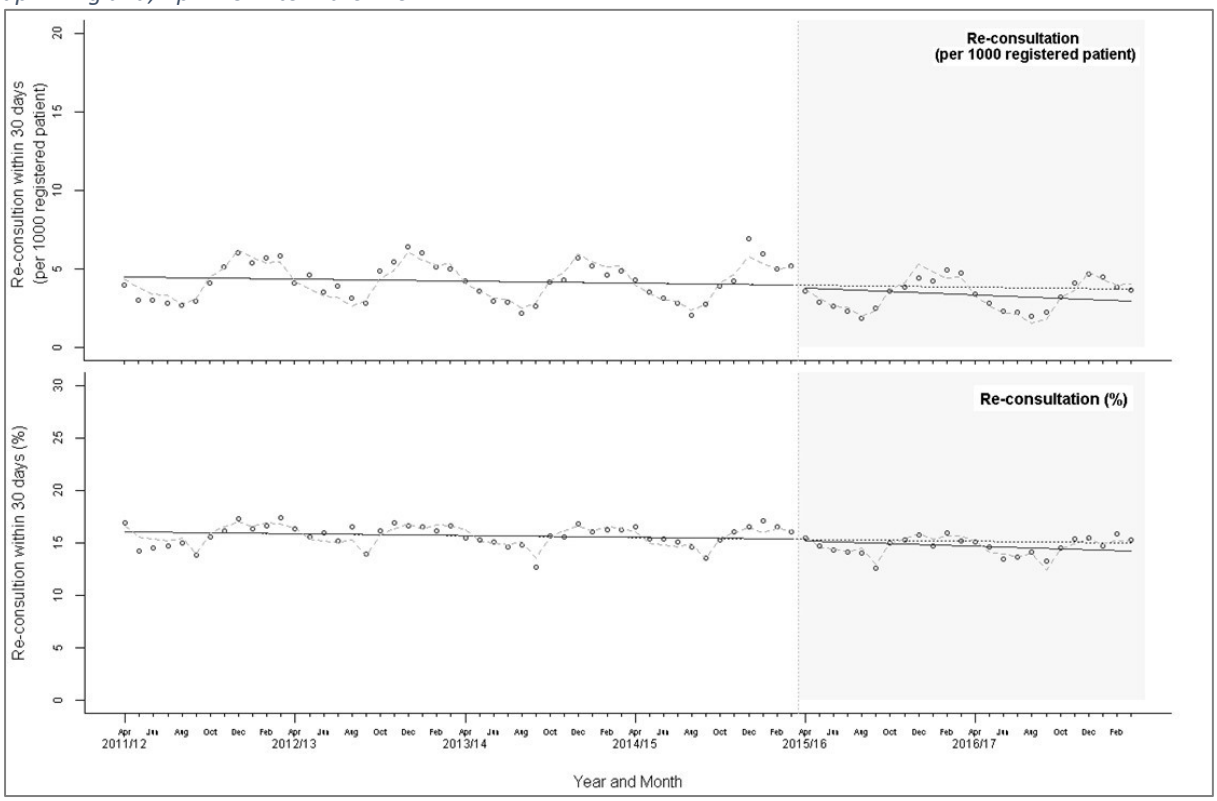


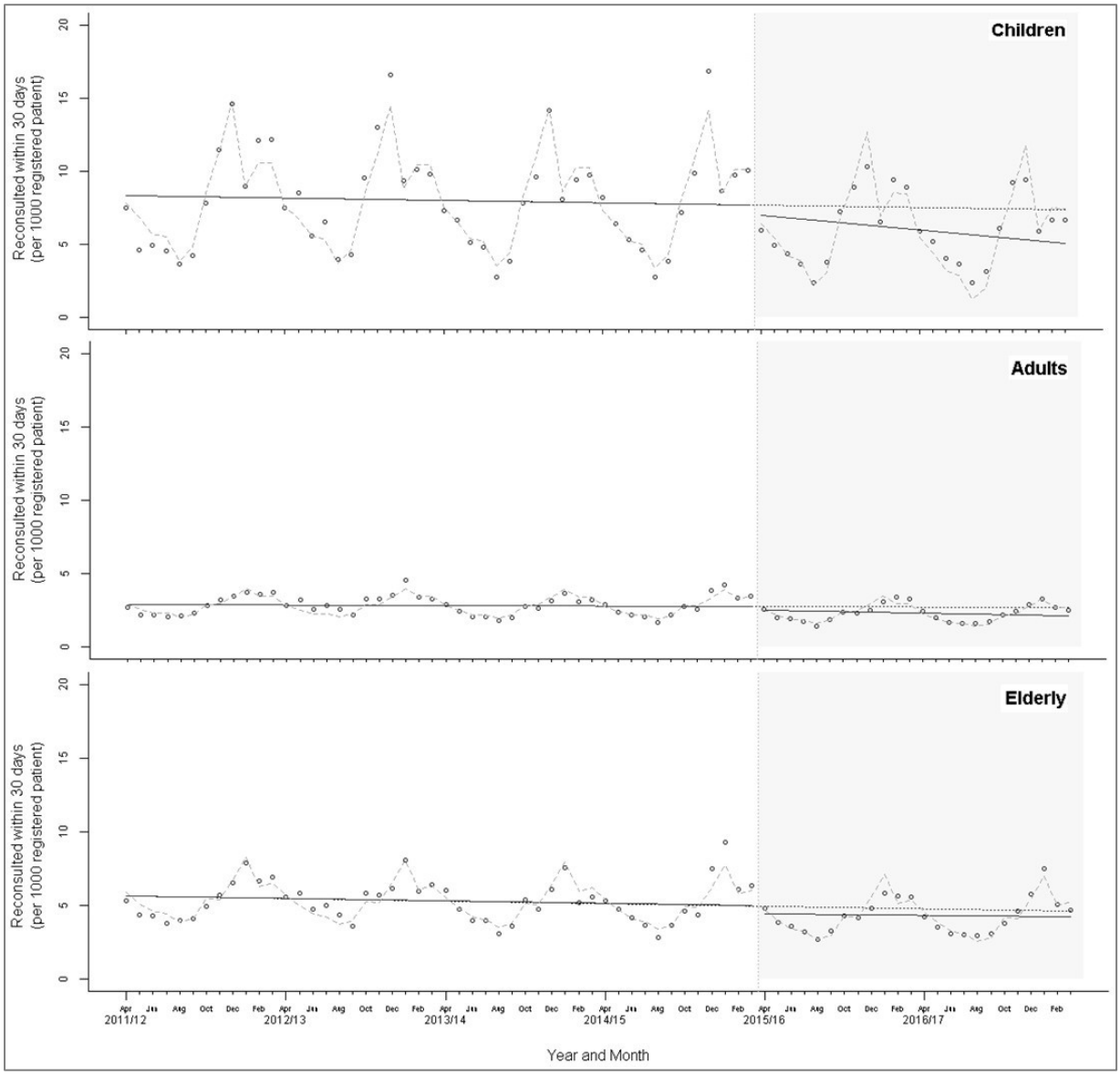
Table 5-2. Re-consultations in primary care: Findings from the interrupted time series analyses on the change in trend and level of re-consultations for uncomplicated RTIs and the relative and absolute changes post-QP

Re-consultations, 2011/12 - 2016/17		**Estimate of intercept**	**Pre-QP trend (*p*-value)**	**Change in level (*p*-value)**	**Change in post-QP trend (*p*-value)**	**Absolute change post 12 months**	**Relative change (%) post 12 months**	**Absolute change post 24 months**	**Relative change (%) post 24 months**
Re-consulted for uncomplicated RTI within 30 days (per 1,000 registered patients)		4.40 (<0.0001)	-0.011 (0.0549)	-0.13 (0.6553)	-0.027 (0.1563)	-0.46	-9	-0.78	-16
Re-consulted for uncomplicated RTI within 30 days (%)		16.62 (<0.0001)	-0.015 (<0.0001)	-0.15 (0.1654)	-0.03 (0.0004)	-0.46	-3	-0.77	-5
Subgroup analyses:									
Age group (per 1,000 registered patients)	Children	7.82 (<0.0001)	-0.01 (0.3759)	-0.65 (0.3809)	-0.07 (0.1272)	-1.49	-15	-2.33	-24
	Adult	2.90 (<0.0001)	-0.0034 (0.5310)	-0.22 (0.2790)	-0.015 (0.3028)	-0.40	-12	-0.58	-18
	Elderly	5.90 (<0.0001)	-0.014 (0.0020)	-0.54 (0.0575)	0.0048 (0.7768)	-0.48	-8	-0.42	-7

5.3.3 Subgroup analysis

Re-consultations amongst children demonstrated the greatest reduction post-QP, compared to adults and the elderly (level decrease of 0.65 per 1000 registered patients, compared with 0.22 in adults and 0.54 in the elderly). However analysis of the TSA by age groups did not exhibit statistically significant changes in the level or trend post-QP (Table 5-2, Figure 5-4).

Figure 5-4. Interrupted time series analyses of the RTI re-consultation rate within 30-day follow-up by age group in England, April 2011 to March 2017



5.4 Results- Study B: Unintended consequences reported in primary care

5.4.1 Trends unintended consequences reported in primary care

Between April 2011 and March 2017, a total of 2,195,414 patients (mean age 36.08 years [SD 27.1 years], age range 0–113 years; women, n = 1,226,766 [55.9%]) who were registered at 431 general practices across England had 5,463,593 episode of infection following an index RTI. Of these infection episodes, 11,865 resulted in the occurrence of a subsequent more severe infection consulted for in

primary care (6,356 [53.6%] complications reported in females, mean age 51.68 [SD 30.8 years], age range 0-106).

Figure 5-5 presents data for RTI episodes and associated complications between April 2011 and March 2017. The observed RTI episodes (per 1,000 registered patient) over the 6-year study period had a stable trend line with a possible slight reduction in 2015/16, with RTI episodes in children and the elderly appearing to reduce over this time period, coinciding with the introduction of the QP. Concurrently, complications (per 100,000 registered patient) reported in primary care show a possible reduction, albeit that complications were very rare, with perhaps greater reductions seen in the elderly (Figure 5-5, Table 5-3). Seasonal peaks in RTI episodes and related complications occurred during the winter period (December to March). RTI episode rates of registered patients over the 6-year study period decreased by 27% from 2011/12 (288.15 per 1,000 registered patients) to 2016/17 (210.69 per 1,000 registered patients). Complications over the study period concurrently decreased (21% decrease, from 60.46 to 47.96 per 100,000 registered patients), although complications by episode rates slightly increased by 8.5% (Table 5-3), although, less than 1% of episodes a month throughout the study period resulted in a complication (Appendix 32, Figure 5-5).

Figure 5-5. The trends in the rate of (a) RTI episodes, (b) rate of complications, and (c) the proportion of RTI episodes which resulted in a complication in England, by age group, April 2011 to March 2017

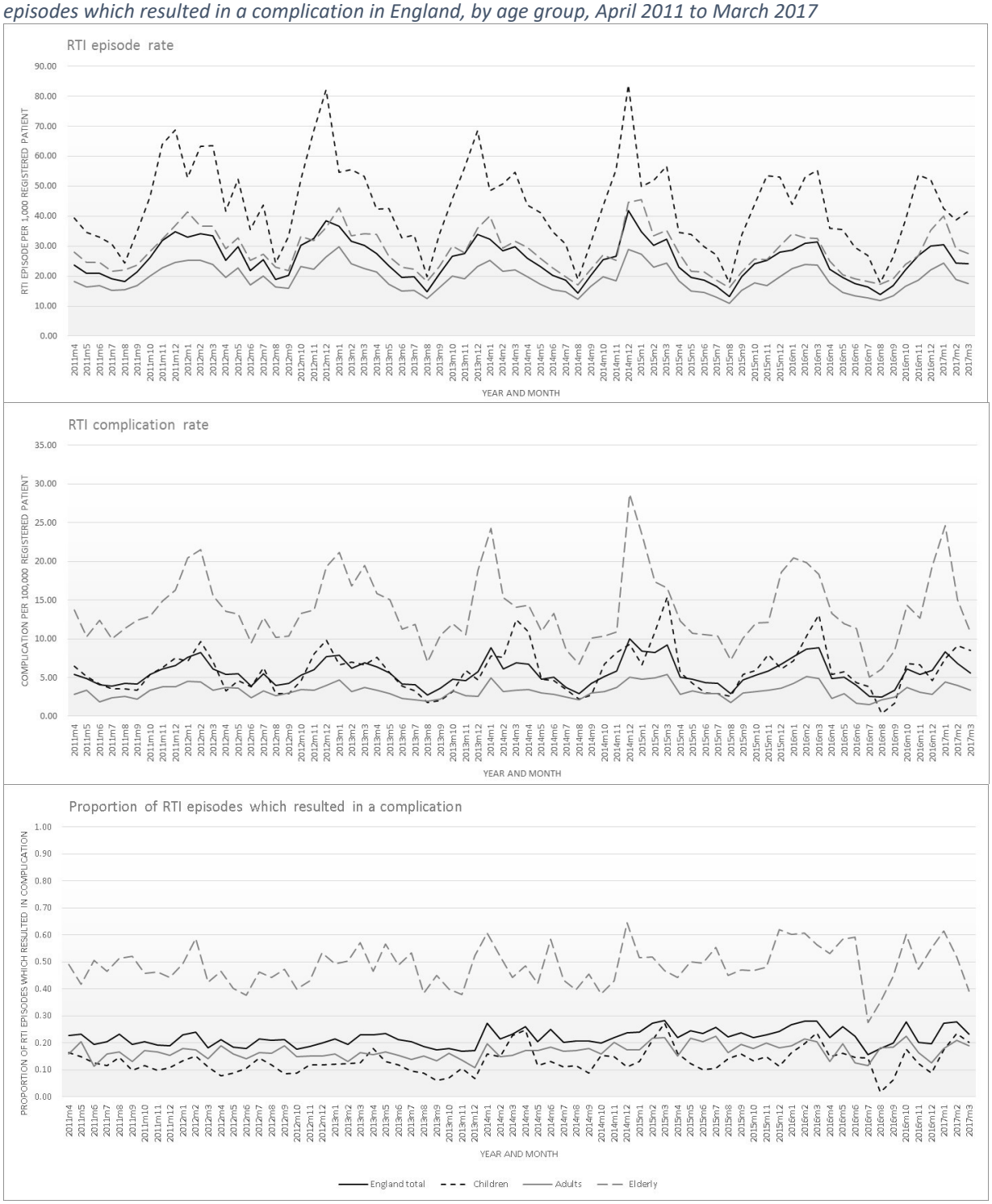


Table 5-3. Complications reported in primary care: Study population and summary of calculated proportions and rates by financial year, April 2011 to March 2017

Parameter	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients	4,235,620	4,100,117	3,895,895	3,439,041	2,832,256	1,949,629
Patients who consulted with an RTI included in study, and had an infectious episode	867,355	902,953	746,748	659,018	452,355	308,025
Total RTI episodes	1,220,507	1,277,152	1,040,012	908,961	606,199	410,762
Count of complications within 30 days of index RTI consultation	2,561	2,564	2,172	2,143	1,490	935
RTI episodes, per 1,000 registered patients	288.15	311.49	266.95	264.31	214.03	210.69
Complications within 30 days, per 100,000 registered patients	60.46	62.53	55.75	62.31	52.61	47.96
Complications within 30 days, per 100,000 RTI episodes	209.83	200.76	208.84	235.76	245.79	227.63

5.4.2 Segmented regression of ITS findings

A slightly increasing linear trend in complications in primary care (per 100,000 registered patients) over the study period can be seen in Figure 5-6. This slight increasing slope of the trend in complications continued post-QP ($p > 0.05$). The graph and model outputs suggest a level drop in complications, corresponding with the introduction of the QP, of 1.04 per 100,000 registered patients ($p < 0.05$), with a corresponding 12% decrease relative to that expected had the existing trend persisted (Table 5-4). Notably, when assessing this change in the level of complications reported in primary care, it is important to understand whether outliers may complicate interpretations of the data. What is apparent, however, is an increase in reported complications in the winter prior to the implementation of the QP, with outliers seen above the trend line (Figure 5-6).

Where complications were assessed based on the underlying RTI episode trend, i.e. rates of complications per 100,000 RTI episodes, the pre-QP trend similarly demonstrated a steady slight increase in complications reported in primary care. However, a level increase in complications, and a decrease in the post-QP slope were noted corresponding with the QP introduction ($p>0.05$) (Figure 5-6, Table 5-4).

Figure 5-6. Interrupted time series analyses of primary care complications within 30-day follow-up in England, April 2011 to March 2017 a) registered patient rate b) RTI episode rate

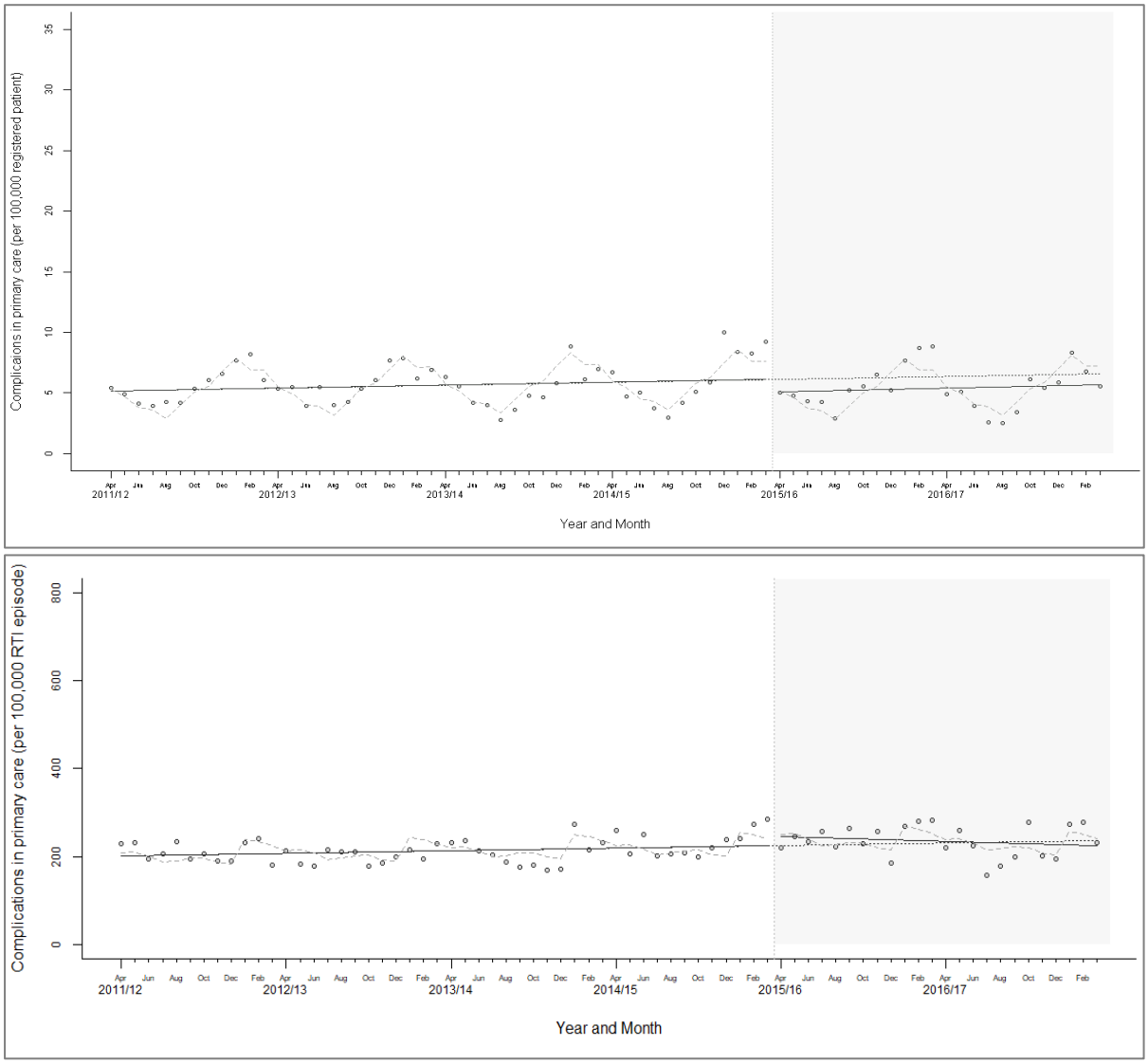
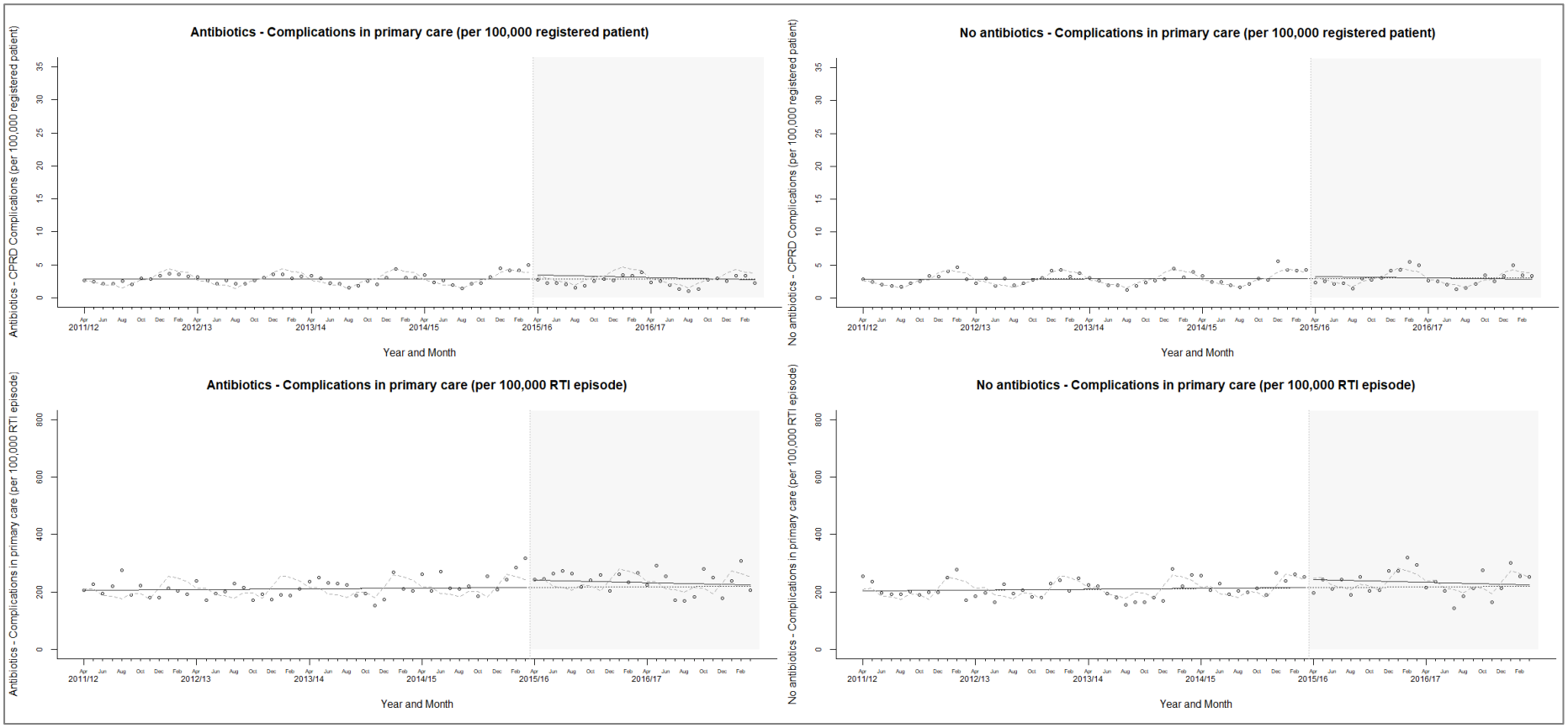


Table 5-4. Complications in primary care: Findings from the interrupted time series analyses on the change in trend and level of complications reported in primary care, and the relative and absolute changes post-QP

CPRD Complications, 2011/12 - 2016/17		Estimate of intercept	Pre-QP trend (*p*-value)	Change in level (*p*-value)	Change in post-QP trend (*p*-value)	Absolute change post 12 months	Relative change (%) post 12 months	Absolute change post 24 months	Relative change (%) post 24 months
Complications within 30 days of an RTI (per 100,000 registered patients)		5.24 (<0.0001)	0.02 (0.0001)	-1.04 (0.0014)	0.0068 (0.6983)	-0.96	-12	-0.88	-11
Complications within 30 days of an RTI (per 100,000 RTI episode)		179.11 (<0.0001)	0.48 (0.1195)	21.69 (0.1163)	-1.41 (0.1041)	4.75	2	-12.20	-5
Sensitivity analyses:									
Complications and index prescribing (per 100,000 registered patients)	Prescribed antibiotics	2.66 (<0.0001)	-0.00064 (0.7791)	0.67 (0.0005)	-0.033 (0.0038)	0.27	7	-0.12	-3
	Not prescribed antibiotics	2.63 (<0.0001)	0.0032 (0.5462)	0.28 (0.2947)	-0.022 (0.1801)	0.02	1	-0.24	-6
Complications and index prescribing (per 100,000 RTI episode)	Prescribed antibiotics	210.34 (<0.0001)	0.19 (0.5191)	25.25 (0.0974)	-0.87 (0.3329)	14.82	6	4.39	2
	Not prescribed antibiotics	209.12 (<0.0001)	0.22 (0.3604)	28.14 (0.0454)	-1.00 (0.2154)	16.08	7	4.03	2
Subgroup analyses:									
Age group (per 100,000 registered patients)	Children	6.01 (<0.0001)	0.027 (0.1545)	-0.46 (0.5564)	-0.07 (0.1665)	-1.30	-11	-2.15	-18
	Adults	2.95 (<0.0001)	0.0094 (0.2987)	-0.28 (0.4715)	-0.025 (0.3342)	-0.58	-13	-0.88	-19
	Elderly	14.59 (<0.0001)	-0.023 (0.0049)	0.43 (0.4483)	-0.035 (0.2909)	0.01	0	-0.41	-3
Age group (per 100,000 RTI episode)	Children	143.57 (0.0007)	0.78 (0.1493)	-12.15 (0.6355)	-0.14 (0.9293)	-13.83	-6	-15.51	-7
	Adults	142.80 (<0.0001)	0.44 (0.1518)	20.11 (0.1752)	-1.47 (0.1072)	2.45	1	-15.21	-8
	Elderly	468.54 (<0.0001)	0.0068 (0.9853)	56.04 (0.0122)	-1.19 (0.3535)	41.73	9	27.42	6
Scarlet fever (per 100,000 registered patients)	Children	0.73 (0.0029)	0.19 (0.0148)	-1.11 (0.2077)	-0.17 (0.3946)	-1.79	-29	-2.46	-36
	Very young children (<9y)	1.55 (0.4112)	0.25 (0.0005)	-0.72 (0.4461)	-0.28 (0.1297)	-1.83	-19	-2.46	-28
Pneumonia (per 100,000 registered patients)	All ages	3.82 (<0.0001)	-0.0084 (0.0018)	0.56 (0.0111)	-0.034 (0.0138)	0.16	4	-0.24	-6
	Children	2.92 (<0.0001)	-0.026 (<0.0001)	0.19 (0.4162)	0.015 (0.2756)	0.37	19	0.55	34
	Adults	1.48 (<0.0001)	0.0101 (0.2478)	-0.48 (0.099)	-0.000905 (0.969)	-0.49	-20	-0.50	-20
	Elderly	12.56 (<0.0001)	-0.0026 (0.8648)	-0.87 (0.2761)	-0.027 (0.5655)	-1.20	-9	-1.52	-11

Figure 5-7. Sensitivity analysis: ITSA of primary care complications within 30-day follow-up in England, April 2011 to March 2017, by patients who were prescribed antibiotics or not at index RTI consultation, calculated as registered patient and RTI episode rates



5.4.3 Sensitivity analysis: Analysis of antibiotic prescribing

Assessment of the trend in complications which occurred in patients who had been prescribed antibiotics, at the index RTI consultation for each episode, compared to those who had not, revealed that complications had been slightly incrementally increasing pre-QP with marginal difference between the two groups (for both the rates by registered patients and by RTI episode) (Table 5-4, Figure 5-7). Introduction of the QP had a correlated increase in the level of complications, again this was seen across both groups, irrespective of whether a patient was prescribed an antibiotic or not. The increase in the level of complications was more prominent in patients who had been prescribed antibiotics (0.67 per 100,00 registered patients, $p<0.05$) compared to those who had not (0.28 per 100,000 registered patients, $p>0.05$. Table 5-4). Assessment by RTI episodes, i.e. those patients who are at risk of a complication, suggested that there were inconsequential differences between patients who were or were not prescribed antibiotics (although those who were not prescribed antibiotics had a slightly greater increase in the level of complications post-QP; 28.14 per 100,000 RTI episode compared with 25.25 per 100,000 RTI episode) and the correlated impact of the QP were predominantly statistically insignificant.

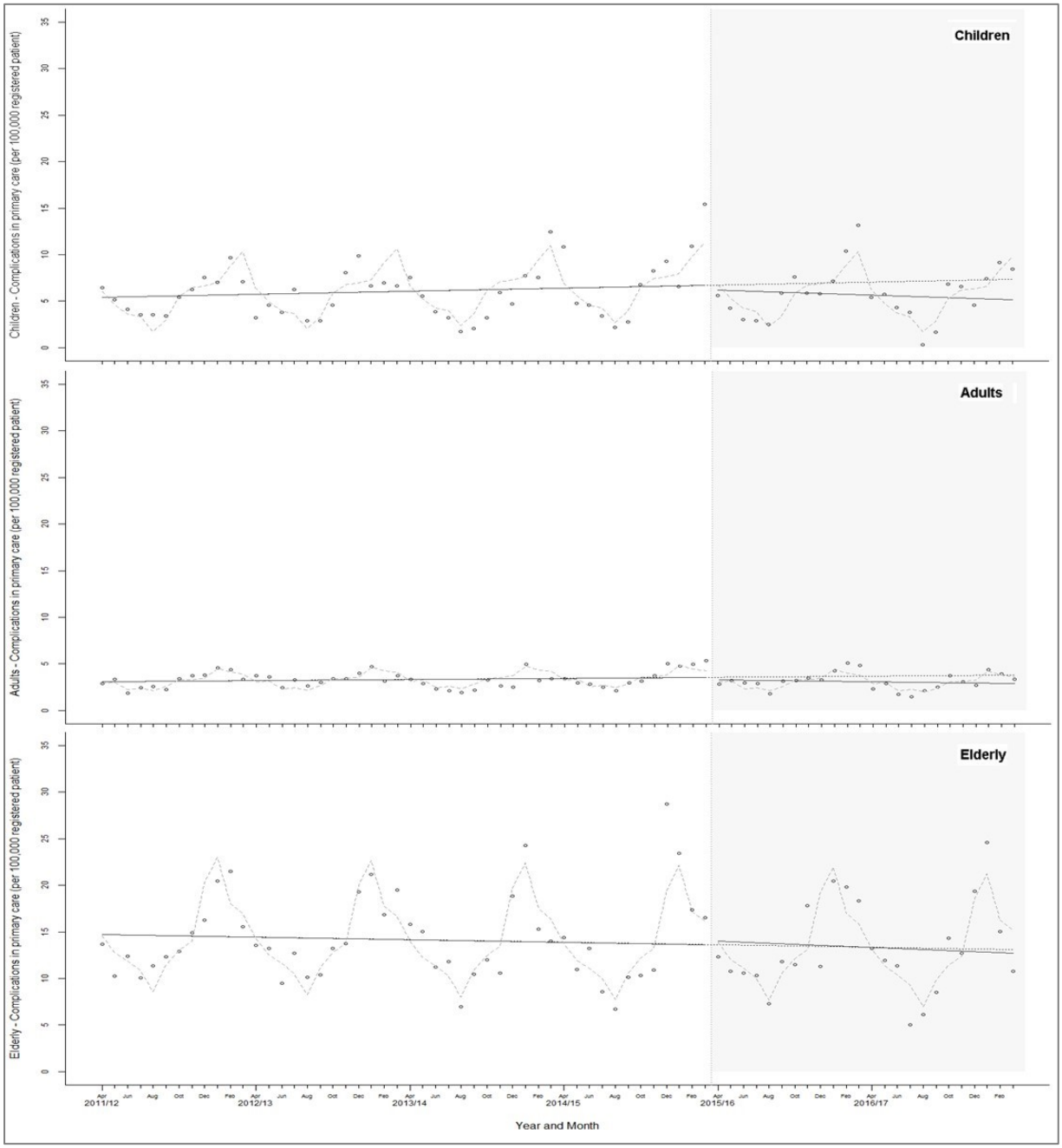
5.4.4 Subgroup analysis

Analysis by age group

The age stratified ITS analysis found no statistically significant change post-QP for any of the age categories, although visually it can be seen that the children exhibited the greatest level decline in complications post-QP (Table 5-4, Figure 5-8, Appendix 33), with an increase in the rate of complications in the elderly (particularly evident with episode rates Appendix 33). There were peaks during the winter period in the complications reported in primary care by age group. Children had an extended seasonality in trends, in that recent years showed peaks in March rather than December.

This could be related to peaks in Scarlet fever in this month in this age category and was investigated further below.

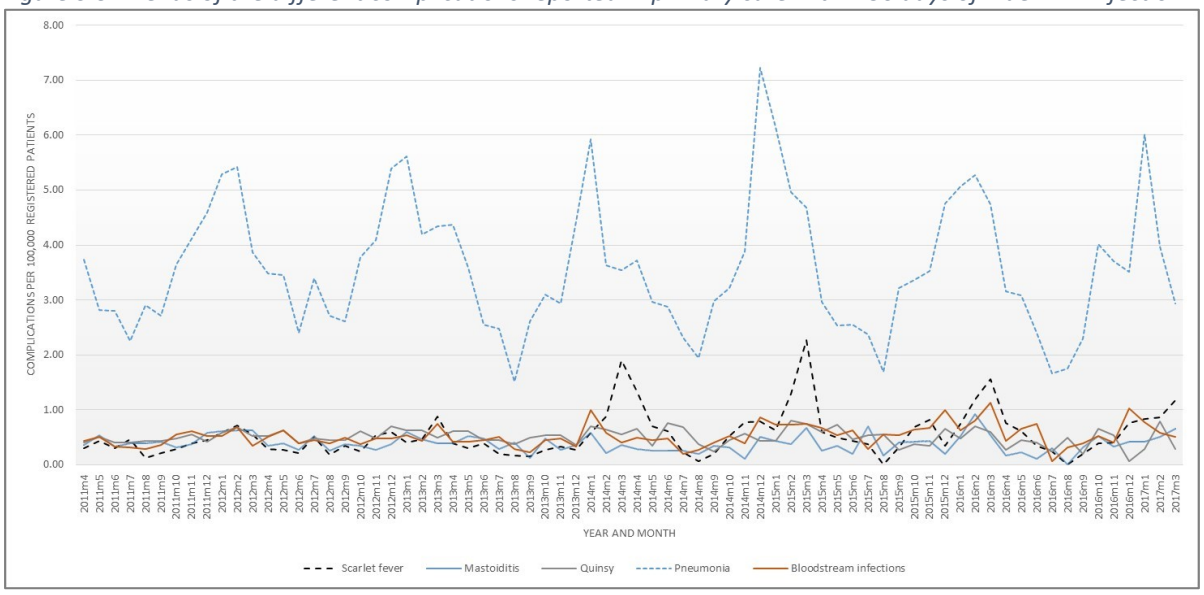
Figure 5-8. Interrupted time series analyses of primary care complications within 30-day follow-up, by age group, April 2011 to March 2017



Assessment of trends by complication group

Of the complications assessed, rheumatic fever, glomerulonephritis, empyema, intracranial abscess and meningitis were extremely rare and were not further considered separately but were included when assessing total complications reported in primary care. Mastoiditis, scarlet fever, quinsy, pneumonia, and BSIs/sepsis were assessed as separate outcomes (Figure 5-9). The most common complications of RTIs reported in general practice were pneumonia and scarlet fever, with on average 36.49 and 5.43 cases of complication per 100,000 registered patient per year respectively (Counts of complications across the study period of 7,638 and 1,096 respectively). These two complication diagnoses were assessed further and where appropriate by age category.

Figure 5-9. Trends of the different complications reported in primary care within 30 days of index RTI infection

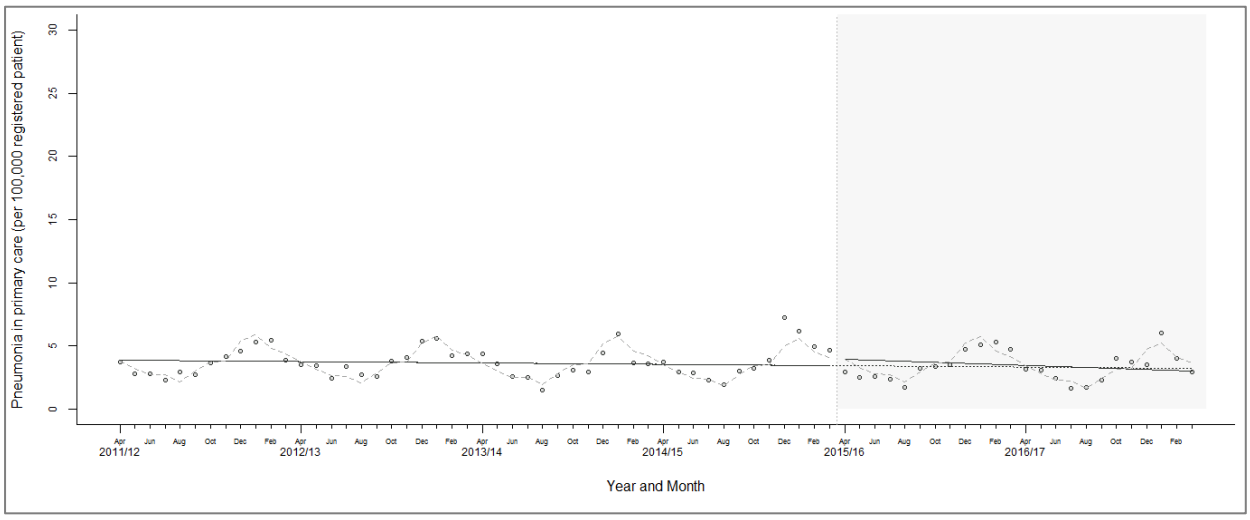


Pneumonia was the most common complication and was particularly evident in the elderly (Appendix 34). The ITS analyses undertaken identified a slight significant level increase in pneumonia (Table 5-4, Figure 5-10) corresponding to the introduction of the QP ($p < 0.05$), although this was accompanied by a statistically significant slight reduction in the post-QP trend of 0.03 per 100,000 registered patients per month ($p < 0.05$). This was also exemplified in that there was a 4% relative increase in primary care

RTI complications 12 months post-QP; however due to the change in the slope 24 months post-QP this was calculated as a decrease of 6% relative to what would have been expected had the pre-QP trend continued.

ITS assessment of pneumonia by age revealed no statistically significant findings, although it was noted that increases in pneumonia rates per 100,000 registered patients was most prevalent in children (Appendix 34).

Figure 5-10. Interrupted time series analyses of primary care pneumonia within 30-day follow-up, April 2011 to March 2017

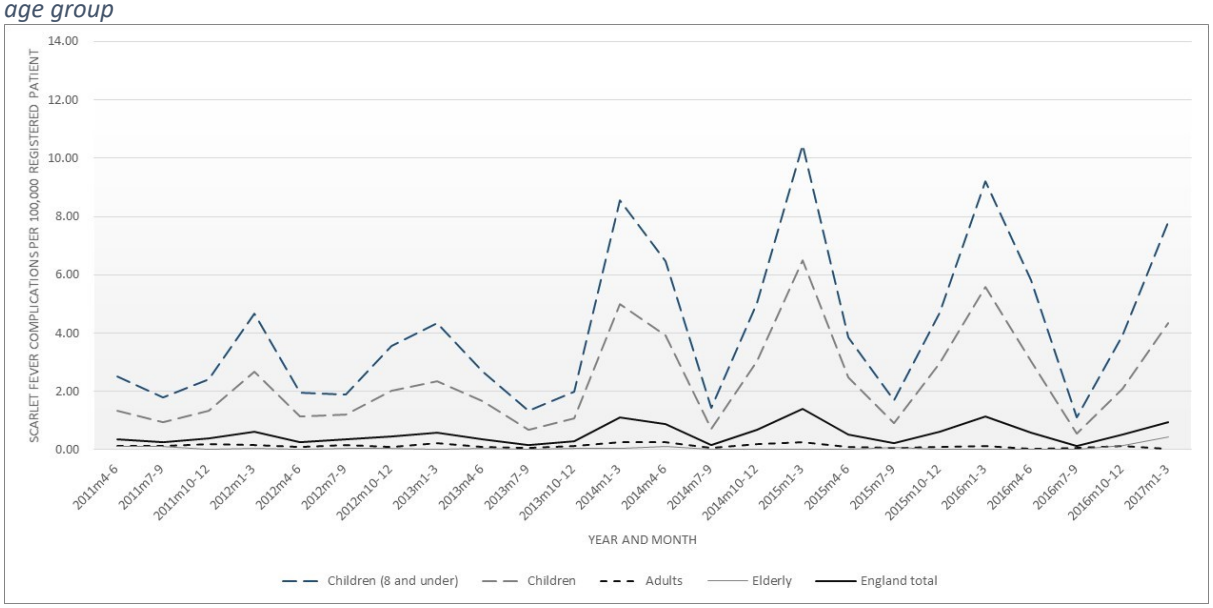


Scarlet fever was the second most prominent complication reported within 30-days in primary care following an uncompleted RTI (Figure 5-9). Scarlet fever was the most common complication reported amongst children in primary care compared to the other complications assessed (Figure 5-11).

Between April 2011 and March 2017, a total of 1,096 episode of infection resulted in scarlet fever following an index RTI (mean age 11 years [SD 14.57 years], age range 0–91 years; women n = 611 [55.8%]). Of these infection episodes which resulted in the occurrence of a subsequent scarlet fever, 81% were reported in children (age range of this age category: 1-15 years: 888 complications, of which 449 were reported in females [50.56%), mean age 5 [SD 2.84 years]), with 71% reported in children

aged eight years and below (781 complications). This greater number of scarlet fever complications is evident in the higher rates seen in children 8 years and under (Table 5-4, Figure 5-12), which was particularly due to higher incidence of scarlet fever occurring in children aged 4 and 5 years. Seasonal trends were evident in the occurrence of scarlet fever as a complication, with annual peaks in the quarters of January-March (quarter 1) and troughs in the quarters of July-September (quarter 3). In 2014 there was a considerable rise in scarlet fever incidence, with the cyclical January-March peaks since 2014 exhibiting a much greater height in scarlet fever as a complication than the preceding years.

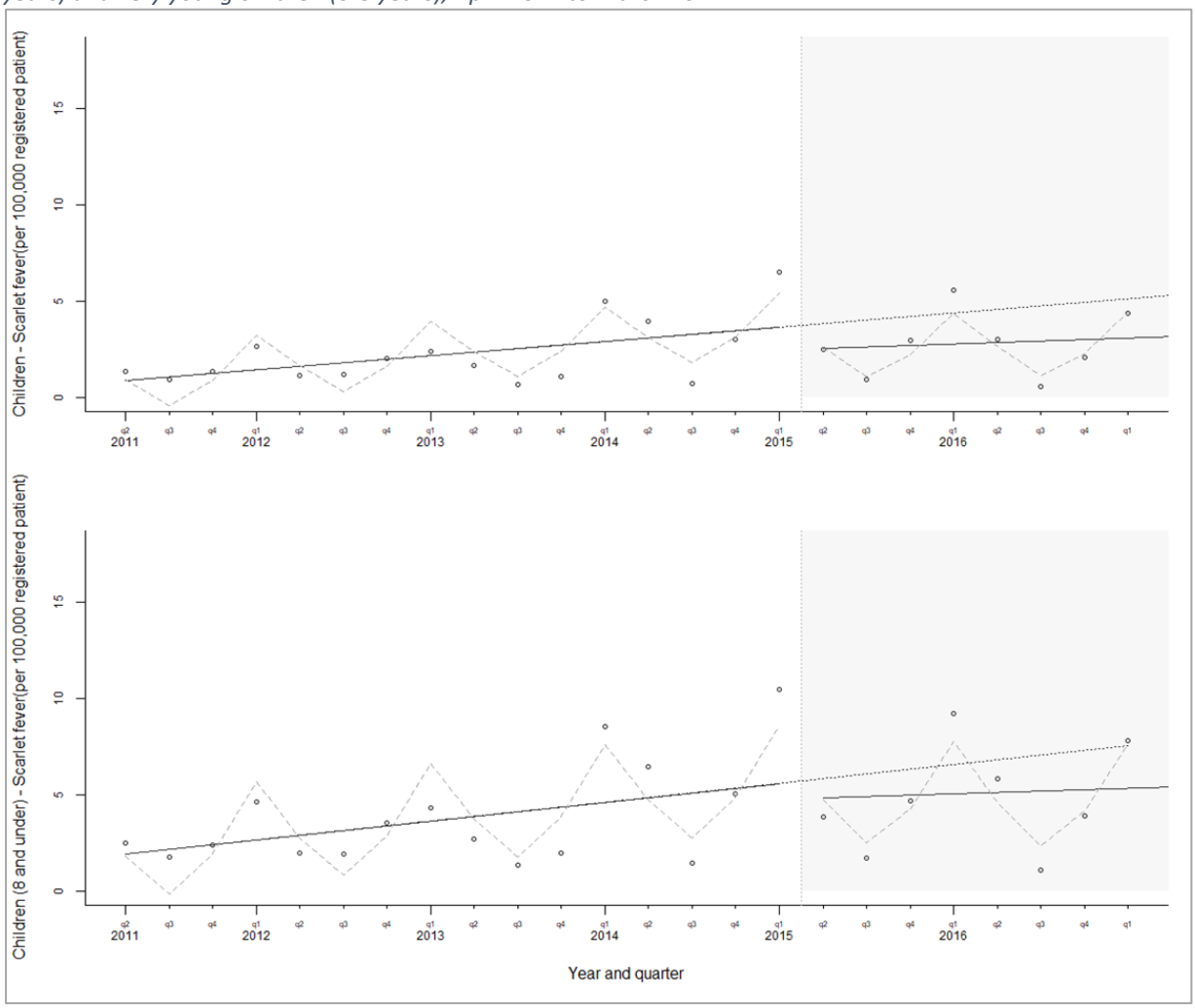
Figure 5-11. Trends of scarlet fever reported in primary care within 30 days of index RTI infection, total and by age group



ITS assessment of the trends in scarlet fever was focused on children (under 16 years of age) only, and as a further sensitivity analysis in the very young (under 9 years). The analysis was completed by quarter due to small cell size counts (Figure 5-12). There was a vast reduction in the level of scarlet fever complications reported in children which coincided with the introduction of the QP, this was also accompanied by a decrease in the post-QP slope in both children and very young children, although these changes were not statistically significant. The trend in scarlet fever pre-QP was increasing by

0.19 per 100,000 registered patients per month ($p < 0.05$) for children aged under 16 years. This increasing trend was more apparent in those under the age of 9 years, with a pre-QP increasing trend of 0.25 per 100,000 registered patients per month ($p < 0.05$). This is likely due to the peaks in January-March 2014 and 2015 (both peaks pre-QP), the corresponding same quarter in 2016 (post-QP) did not exceed these two previous peaks.

Figure 5-12. Interrupted time series analyses of scarlet fever consultations in primary care with children (0-15 years) and very young children (0-8 years), April 2011 to March 2017



5.5 Results- Study C: Unintended consequences reported in HES data

5.5.1 Trends unintended consequences reported in secondary care

A high proportion of CPRD general practice registered patients (80%, 4,330,499/5,436,557) were eligible for linkage to HES data. Of the patients who consulted with an uncomplicated RTI during the study period of April 2011 – March 2017, 80% (1,762,490/2,195,414 patients) were eligible for HES linkage.

Table 5-5 displays the count of hospital admissions for the complications of interest in this study, with a breakdown of complications as reported by the primary diagnosis code alone, which captured 56% of complications, and by all other ICD-10 codes for complications reported within the first episode of a first spell of hospital admission. This permitted the reporting of a further 44% of complications which would have been missed had these other admission codes not been incorporated within the analyses.

The coding/reporting of different complications by year were captured using a patients' hospital admission's primary diagnosis and by first episode codes. As can be seen in Table 5-6 BSIs where coded were not frequently captured as the primary diagnosis code, with only 18% of ICD-10 codes for patients admitted with a BSI being captured within the primary diagnosis code variable. Pneumonia and quinsy on the other hand, where reported, were often coded as the primary diagnosis code. To increase sensitivity, the analyses therefore focused on all first episode ICD-10 codes and not the singular primary diagnosis code.

Table 5-5. ICD-10 hospital admissions for a complication within 30 days, between April 2011 to March 2017, by primary diagnosis code and all other first episode codes.

Year	Primary diagnosis ICD-10 code (%)		All other first episode ICD-10 codes (%)		Total first episode ICD-10 codes
2011/12	1134	(54)	960	(46)	2094
2012/13	1233	(56)	984	(44)	2217
2013/14	1063	(56)	840	(44)	1903
2014/15	1004	(57)	759	(43)	1763
2015/16	688	(56)	541	(44)	1229
2016/17	419	(55)	344	(45)	763
Total	5541	(56)	4428	(44)	9969

Table 5-6. First episode ICD-10 codes and primary ICD-10 diagnosis code for hospital admissions of complications within 30 days, by complication group

	2011/12		2012/13		2013/14		2014/15		2015/16		2016/17		Total	
Complication	1st epi	1° diag	1st epi	1° diag	1st epi	1° diag	1st epi	1° diag	1st epi	1° diag	1st epi	1° diag	First episode codes	Primary diagnosis code (%)
BSIs	598	89	626	110	515	102	447	90	336	95	214	43	2,736	529 (18)
Empyema	36	20	35	21	27	19	20	12	21	13	11	8	150	93 (61)
Pleurisy	594	116	628	130	543	95	526	90	387	70	251	43	2,929	544 (19)
Pneumonia	1,035	779	1,136	839	931	703	903	669	617	432	377	267	4,999	3,689 (74)
Quinsy	165	140	160	133	181	146	162	129	107	80	76	61	851	689 (81)
*Other**	*31*	*15*	*44*	*23*	*34*	*19*	*33*	*23*	*22*	*14*	*12*	*8*	*176*	*102 (58)*
Otitis Media	68	42	69	45	62	24	53	29	27	15	27	14	306	169 (55)
Upper RTI	371	237	390	246	372	234	325	204	228	142	121	69	1,807	1,132 (63)
Lower RTI	1,766	1,040	1,886	1,136	1,542	901	1,459	857	938	548	714	438	8,305	4,920 (60)

*Other: Small cell size of certain complications have been combined: glomerulonephritis, intracranial abscess, meningitis, rheumatic fever, scarlet fever, mastoiditis

Note: More than one complication may have been coded for the same patient within the same episode in this table, when assessed as total complications duplicate within episode complications would not be counted

As mentioned in section 5.4, similar trends were observed across the study period of a decrease in registered patients (of those who were eligible for HES linkage) and patients consulting with an RTI. The underlying basis for the reduction was also seen in the RTI episodes assessed (Table 5-7). Hospital admissions for the complications studied, appears to have reduced between 2011/12 and 2016/17 (18% decrease, from 61.50 to 50.14 per 100,000 registered patients eligible for data linkage) (Table 5-7). However, for patients who consulted, there was an 11% increase in hospital admission for complications (2.12 to 2.35 per 1,000 RTI episode), albeit that complications/hospital admission were rare, with less than 0.3% of uncomplicated RTI episodes resulting in hospital admissions for more severe infections in any year studied. Hospital admissions following an index RTI consultation in

primary care were more evident in the elderly, who had higher counts and rates of hospital admissions for complications (Appendix 36).

Table 5-7. Complications in secondary care: Study population and summary of calculated proportions and rates by financial year, April 2011 to March 2017

Parameter	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients who were eligible for HES linkage	3,405,119	3,282,352	3,113,263	2,698,669	2,193,349	1,521,760
RTI patients who consulted with an infectious episode (30-day follow-up)	867,355	902,953	746,748	659,018	452,355	308,025
RTI patients with an infectious episode, who were eligible for HES linkage (%)	701,350 (81)	728,367 (81)	598,554 (80)	519,548 (79)	356,140 (79)	244,349 (79)
Total RTI episodes of patients eligible for HES linkage	986,281	1,028,950	832,188	714,899	475,858	324,442
Hospital admission for complications of interest within 30 days of index RTI - 1˚ diagnosis code	1,134	1,233	1,063	1,004	688	419
Hospital admission for complications of interest within 30 days of index RTI - 1st hospital episode codes	2,094	2,217	1,903	1,763	1,229	763
Hospital admissions within 30 days, per 100,000 registered patients (eligible for linkage)	61.50	67.54	61.13	65.33	56.03	50.14
Hospital admissions within 30 days, per 1,000 RTI episode	2.12	2.15	2.29	2.47	2.58	2.35

5.5.2 Segmented regression of ITS findings

The pre-QP trend for hospital admissions due to complications following an RTI was relatively linear (slightly decreasing by 0.02 per 100,000 registered patients, $p<0.05$). Subsequent to the introduction of the QP, this trend further decreased by 0.083 per 100,000 registered patients ($p<0.05$), with an additional slight level decrease the month the QP was introduced ($p>0.05$). Twelve months after the introduction of the QP, the average monthly hospital admission for RTI complications was 1.0 per 100,000 registered patient less than what would have been expected had the pre-QP trend continued (Table 5-8, Figure 5-13).

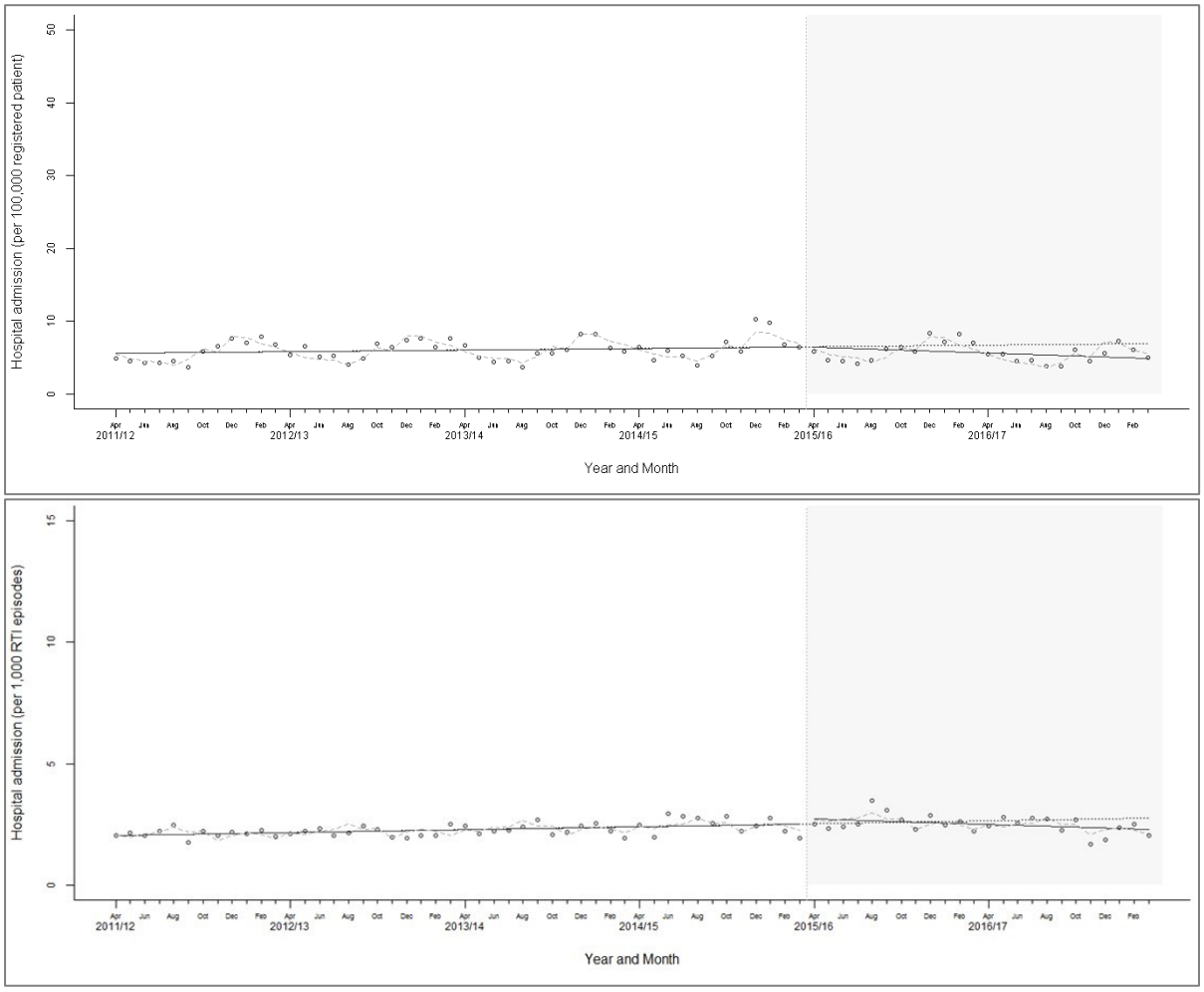
The findings from the ITSA of complication rates by RTI episodes suggests a level increase in hospital admissions for RTI complications associated with the QP ($p>0.05$), and a decrease in the post-QP trend

of 0.03 per 1,000 RTI episodes (p<0.05). Similarly to the rates based on registered patients, 12 months post-QP this represented a relative decrease to that expected based on the counterfactual trend, although this was a smaller relative decrease of 5% compared to 14% (Table 5-8, Figure 5-13).

Table 5-8. Complications in secondary care: Findings from the interrupted time series analyses on the change in trend and level of hospital admissions for complications, and the relative and absolute changes post-QP

Hospital admissions, 2011/12 - 2016/17		**Estimate of intercept**	**Pre-QP trend (p-value)**	**Change in level (p-value)**	**Change in post-QP trend (p-value)**	**Absolute change post 12 months**	**Relative change (%) post 12 months**	**Absolute change post 24 months**	**Relative change (%) post 24 months**
Hospital admissions for complications within 30 days of an acute RTI (per 100,000 patients)		5.44 (<0.0001)	0.02 (0.0509)	-0.0033 (0.9941)	-0.083 (0.0027)	-1.00	-14	-1.99	-27
Hospital admissions for complications (per 1,000 RTI episode)		2.01 (<0.0001)	0.01 (0.0010)	0.22 (0.1278)	-0.028 (0.0020)	-0.11	-5	-0.45	-18
Subgroup analyses:									
Age group (per 100,000 CPRD registered patients)	Children	1.91 (<0.0001)	0.011 (0.2638)	-0.0016 (0.9971)	-0.032 (0.2546)	-0.38	-9	-0.76	-18
	Adults	2.25 (<0.0001)	0.0093 (0.0287)	-0.21 (0.3504)	-0.018 (0.1831)	-0.43	-14	-0.64	-20
	Elderly	21.05 (<0.0001)	-0.025 (0.5377)	0.73 (0.7144)	-0.301 (0.0143)	-2.89	-11	-6.50	-26
Age group (per 1,000 RTI episodes)	Children	0.42 (0.0015)	0.0038 (0.0554)	0.0032 (0.9729)	-0.0016 (0.7745)	-0.02	-2	-0.04	-4
	Adults	1.03 (<0.0001)	0.007 (<0.0001)	-0.016 (0.8696)	-0.0055 (0.3262)	-0.08	-6	-0.15	-10
	Elderly	6.65 (<0.0001)	0.022 (0.1435)	1.14 (0.1155)	-0.11 (0.0134)	-0.19	-2	-1.52	-19
By complication: BSI	(per 100,000 patients)	1.77 (<0.0001)	-0.0019 (0.0961)	-0.035 (0.6553)	0.0062 (0.1814)	0.04	3	0.11	10
	(per 1,000 RTI episodes)	0.63 (<0.0001)	0.0016 (<0.0001)	-0.0026 (0.8771)	0.0047 (0.0001)	0.05	13	0.11	26
By complication: Pneumonia	(per 100,000 patients)	3.64 (<0.0001)	0.0084 (0.0216)	-0.19 (0.3150)	-0.015 (0.1831)	-0.38	-13	-0.56	-18
	(per 1,000 RTI episodes)	1.35 (<0.0001)	0.0067 (<0.0001)	-0.039 (0.0280)	-0.0026 (0.0566)	-0.07	-7	-0.10	-9
Sensitivity analyses:									
Hospital admissions and index prescribing (per 100,000 registered patients)	Prescribed antibiotics	2.69 (<0.0001)	0.0028 (0.3561)	0.096 (0.5406)	-0.037 (0.0003)	-0.34	-11	-0.78	-24
	Not prescribed antibiotics	1.86 (<0.0001)	0.00208 (0.0989)	0.083 (0.4256)	-0.02008 (0.0029)	-0.16	-7	-0.40	-17
Hospital admissions and index prescribing (per 1,000 RTI episode)	Prescribed antibiotics	1.85 (<0.0001)	0.0094 (<0.0001)	0.44 (<0.0001)	-0.028 (<0.0001)	0.10	5	-0.24	-10
	Not prescribed antibiotics	1.41 (<0.0001)	0.0051 (<0.0001)	-0.0089 (0.9065)	-0.013 (0.0039)	-0.17	-11	-0.33	-20
Hospital admissions based on primary ICD-10 code (per 100,000 CPRD registered patients)		5.51 (<0.0001)	0.016 (0.0537)	-0.11 (0.7886)	-0.083 (0.0012)	-0.89	-12	-1.89	-26

Figure 5-13. Interrupted time series analysis of hospital admissions for complications within 30-day follow-up in England a) per 100,000 registered patients, b) per 1,000 RTI episodes, April 2011 to March 2017



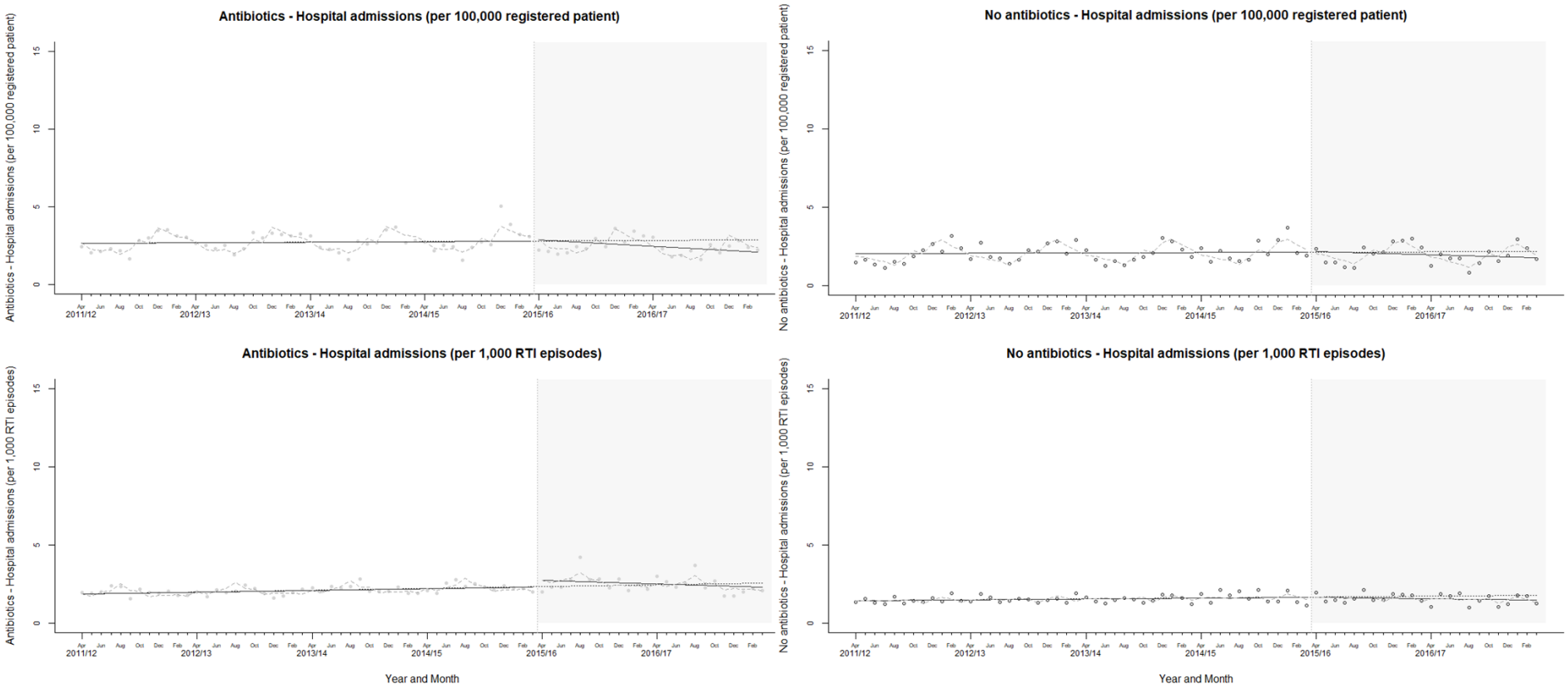
5.5.4 Sensitivity analysis

Analysis of antibiotic prescribing

Assessment of the trends in secondary care complications, stratified as to whether patients had been prescribed antibiotics or not at the index RTI consultation, demonstrated a very slightly increasing trend pre-QP (for both prescribed and not prescribed, and both registered patient and episode rates) (Figure 5-14, Table 5-8). The rates were increasing to a slightly greater extent in patients who had been prescribed antibiotics. With the introduction of the QP, there was a correlated level increase in complications for patients who had been prescribed antibiotics (this was statistically significant in the prescribed antibiotics per 1,000 RTI episode). Where the rates by episodes were considered, those who were not prescribed antibiotics had a level ($p>0.05$) and trend decrease ($p<0.05$) in complications.

Twelve months after the QP, the average monthly antibiotic prescribing rate showed a correlated decrease in complications across both patients who were prescribed and those who were not prescribed antibiotics. This was the case for all rates assessed stratified by antibiotic use at index RTI consultation, apart from the episode rate for patients who were prescribed antibiotics. These patients had an average monthly complication rate which was 0.1 per 1,000 RTI episode greater than would have been expected had the QP not been introduced, representing a 5% increase relative to that expected had the existing trend continued.

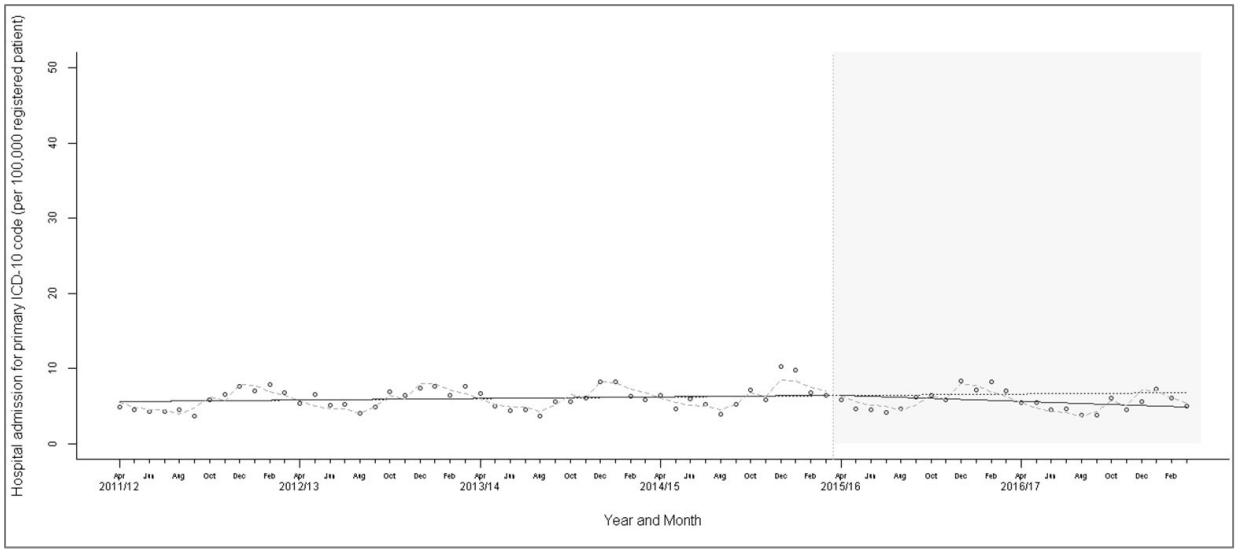
Figure 5-14. Sensitivity analysis: ITSA of hospital admissions for complications within 30-day in England, April 2011 to March 2017, by patients who were prescribed antibiotics or not at index RTI consultation, calculated as registered patient and RTI episode rates



Analysis of the primary diagnosis for hospital admissions

Assessment of hospital admissions for RTI complications using the primary diagnosis ICD-10 only demonstrated similar level and trend decreases associated with the introduction of the QP, compared to all first hospital episode ICD-10 codes (Table 5-8, Figure 5-15).

Figure 5-15. Interrupted time series analyses of the primary diagnosis hospital admissions for complications within 30-day follow-up in England (per 100,000 registered patients), April 2011 to March 2017



5.5.3 Subgroup analysis

Analysis by age group

The age stratified ITSA showed similar associations to the QP, in that the level and trend in hospital admissions for RTI complications for all age categories generally decreased post-QP, based on registered patients. However, all were statistically insignificant apart from the decreasing trend post-QP in the elderly (Figure 5-16). The elderly age category exhibited an increase in the level of hospital admissions for RTI complications coinciding with the QP introduction, of 0.73 per 100,000 registered patients (p>0.05) (Table 5-8).

Age stratified findings by RTI episodes suggest an increase in admissions due to complication in children and the elderly, although both these changes were not statistically significant. Similar to the

previous age-stratified ITSA, trends in hospital admissions were increasing prior to the QP amongst all age categories, with the greatest seasonal fluctuations and highest rates seen in the elderly (Appendix 37).

Assessment of trends by complication

Hospital admissions for RTI indications, which included ICD-10 codes for upper RTIs, lower RTIs and AOM, were relatively unchanged pre- and post-QP, further evaluation of these trends was therefore not undertaken.

As many of the complications investigated were rare, throughout the analyses the complications were assessed as one outcome per RTI infectious episode for each patient. The hospital admissions observed per month for BSIs and pneumonia were evaluated separately. Both rates, calculated based on registered patients or based on the underlying RTI episode counts, displayed decreasing trends and levels associated with the introduction of the QP for pneumonia hospital admissions; these decreases were statistically significant for rates calculated per 1,000 RTI episodes (0.04 decrease in level and 0.003 decreasing trend, $p < 0.05$) (Table 5-8). Hospital admissions for BSIs demonstrated an increase, albeit these findings were predominantly statistically insignificant. Following the introduction of the QP in April 2015, there was a slight level decrease (of 0.04 per 100,000 registered patients) in hospital admissions for BSIs within a 30-day RTI episode. There was however an associated increase in the post-QP trend for BSI outcomes of 0.006 per 100,000 registered patients ($p > 0.05$, with an increase of 0.005 per 1,000 RTI episodes [$p<0.05$]). Twelve months post-intervention, the average monthly BSI hospital admission within a 30-day RTI episode was 0.04 per 100,000 registered patients more than would have been expected had the QP not been introduced. This represents a 3% increase relative to that expected based on the counterfactual trend (Table 5-8, Figure 5-17).

Figure 5-16. Interrupted time series analyses of hospital admissions for complications within 30-day follow-up, by age group (per 100,000 registered patients), April 2011 to March 2017

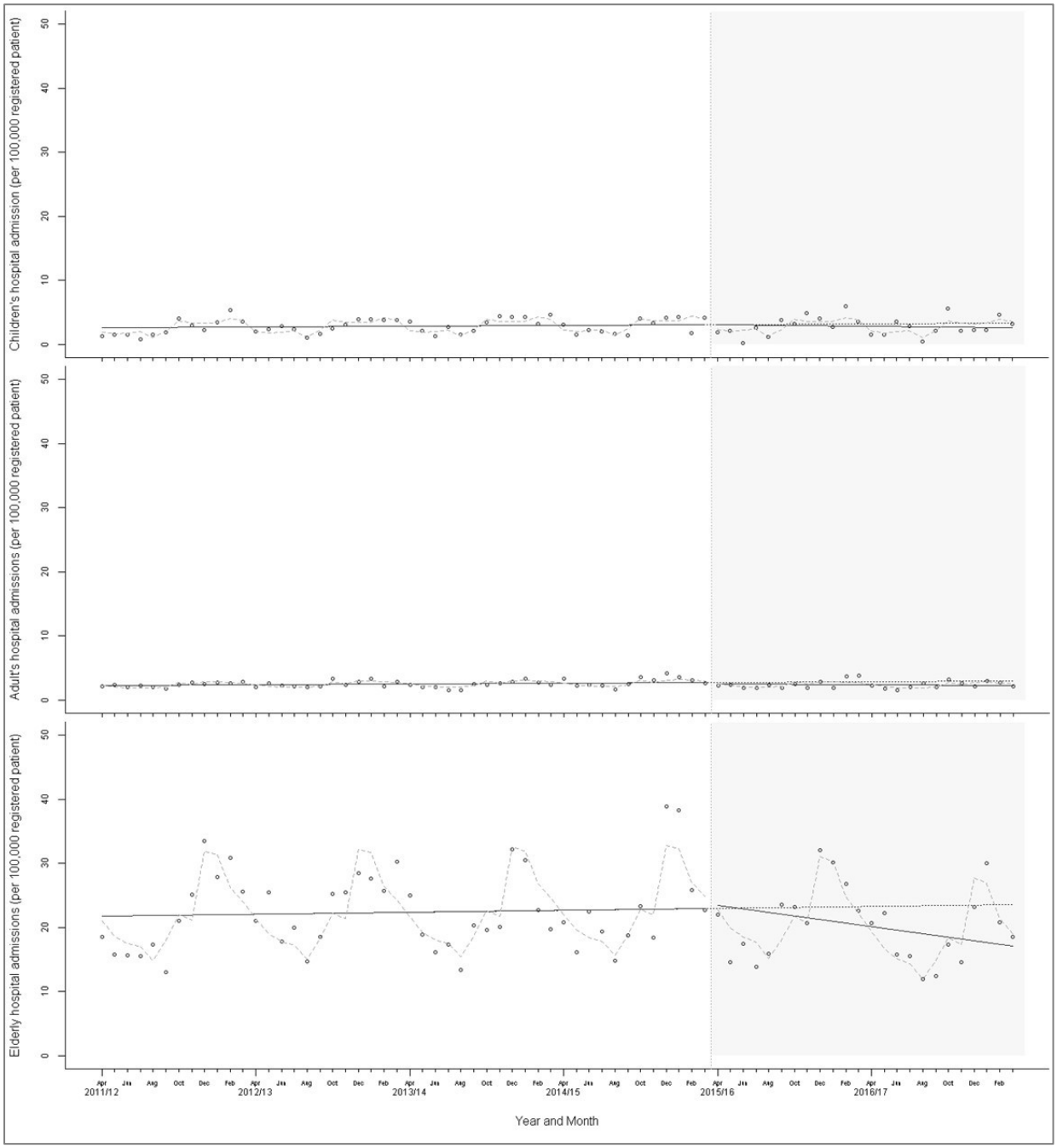
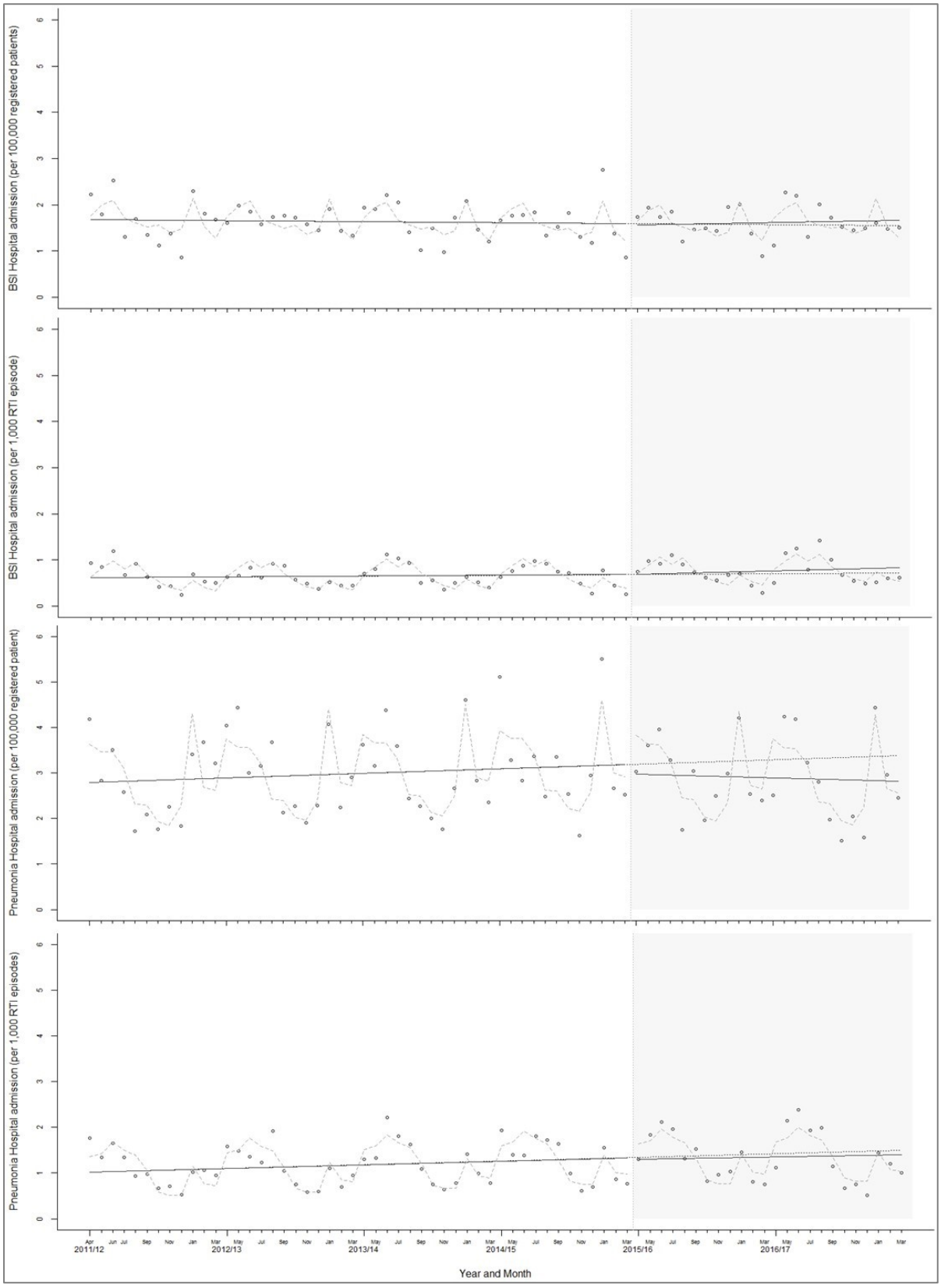


Figure 5-17. Interrupted time series analyses of hospital admissions for BSI and pneumonia complications within 30-day follow-up (per 100,000 registered patients and per 1,000 RTI episodes), April 2011 to March 2017



5.6 Results- Study D: Unintended consequences reported in ONS mortality data

5.6.1 Trends in mortality following an uncomplicated RTI

A high proportion of CPRD general practice registered patients (80%, 4,330,499/5,436,557) were eligible for linkage to ONS data. Of the patients who consulted with an uncomplicated RTI during the study period of April 2011 – March 2017, 80% (1,762,490/2,195,414 patients) were eligible for ONS linkage.

Of the total index RTI consultations 9,893 resulted in mortality within 30 days, 3,882 (39% of all-cause mortality) of these were coded as mortality related to the complications assessed in this research i.e. had an ICD-10 code of an infectious complication (Table 5-9). The vast majority of all-cause mortality and mortality specifically related to complications occurred in the elderly (all-cause mortality: 90%, 8,857; mortality coded as complication: 93%, 3,619), with very low mortality observed in children (43, 0.4% of all-cause mortality assessed). Mortality rates, per 100,000 registered patient and per 1,000 RTI episode, were higher in elderly patients (Appendix 38).

Trends in mortality rate following an index uncomplicated RTI were measured by all-cause mortality within 30 days. All-cause mortality rates, per 100,000 registered patients and per 1,000 RTI episodes, decreased over the 6-year study period by 42% (from 67.63 to 39.49 per 100,000 registered patient) and 21% (from 2.34 to 1.85 per 1,000 RTI episodes) respectively (Table 5-9). This reduction in mortality rates was paralleled in the elderly mortality rates across the study period (Appendix 38).

Table 5-9. All-cause mortality: Study population and summary of calculated rates by financial year, April 2011 to March 2017

Parameter	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients who were eligible for ONS linkage	3,405,119	3,282,352	3,113,263	2,698,669	2,193,349	1,521,760
Total RTI episodes of patients eligible for ONS linkage	986,281	1,028,950	832,188	714,899	475,858	324,442
All-cause mortality within 30 days of index RTI	2,303	2,388	1,831	1,730	1,040	601
Mortality related to infectious complication within 30 days of index RTI	919	1,031	686	676	369	201
All-cause mortality within 30 days, per 100,000 registered patients	67.63	72.75	58.81	64.11	47.42	39.49
All-cause mortality within 30 days, per 1,000 RTI episodes	2.34	2.32	2.20	2.42	2.19	1.85

5.6.2 Segmented regression of ITS findings

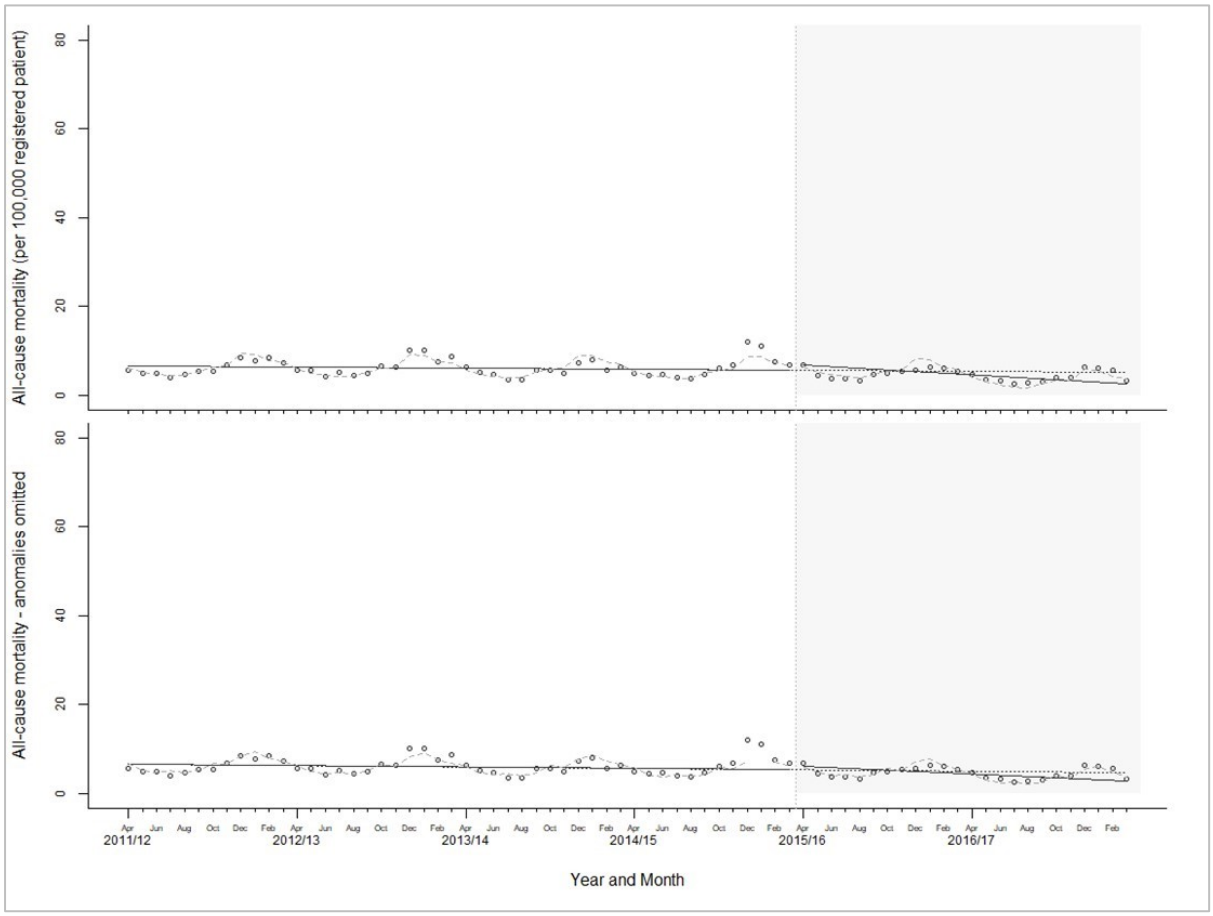
30-day all-cause mortality for patients who had consulted with an RTI in primary care had been slightly decreasing pre-QP, by 0.019 deaths per 100,000 registered patients per month (p<0.05). This decreasing slope showed further reduction coinciding with the introduction of the QP (by 0.17 deaths per 100,000 registered patients per month, p<0.05). Alongside this decreasing trend however, there was an increase in the level by 1.19 per 100,000 registered patients (p<0.05) (Figure 5-18). Twelve months after the QP, the average monthly mortality rate within 30-days of an index RTI was 0.81 per 100,000 registered patients less than would have been expected had the QP not been introduced, representing a 12% decrease relative to that expected had the pre-QP trend continued (Table 5-10).

Potential outliers in the data were omitted as part of a sensitivity analysis. The December 2014 and January 2015 data were higher than in the corresponding months of previous years and appeared as "wild points" amongst the trend. This analysis reduced the level increase seen in relation to the introduction of the QP, to 0.77 (rather than 1.19) per 100,000 registered patients. The steepness of the slope post-QP was also reduced to 0.11 deaths per 100,000 registered patients (Figure 5-18).

Table 5-10. Findings from the interrupted time series analyses on the change in trend and level of mortality within 30-days of an index uncomplicated RTI, and the relative and absolute changes post-QP

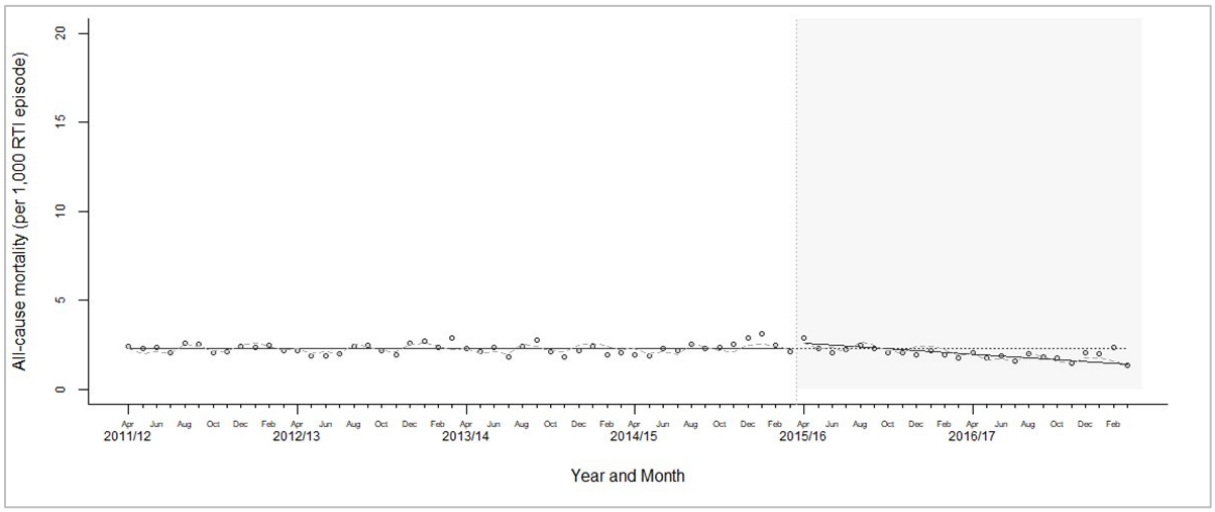
Mortality, 2011/12 - 2016/17		**Estimate of intercept**	**Pre-QP trend (*p*-value)**	**Change in level (*p*-value)**	**Change in post-QP trend (*p*-value)**	**Absolute change post 12 months**	**Relative change (%) post 12 months**	**Absolute change post 24 months**	**Relative change (%) post 24 months**
All-cause mortality within 30 days of an acute RTI (per 100,000 patients)		6.25 (<0.0001)	-0.019 (0.0042)	1.19 (0.0071)	-0.17 (<0.0001)	-0.81	-12	-2.80	-43
All-cause mortality within 30 days of an acute RTI (per 1,000 RTI episodes)		2.31 (<0.0001)	-0.00016 (0.7800)	0.38 (<0.0001)	-0.052 (<0.0001)	-0.25	-11	-0.88	-39
Sensitivity analyses:									
Omitting anomalies	All-Cause mortality (/100,000 patients)	6.83 (<0.0001)	-0.026 (0.0001)	0.77 (0.0411)	-0.11 (<0.0001)	-0.56	-9	-1.89	-33
	Mortality in the elderly (/100,000 patients)	33.22 (<0.0001)	-0.19 (<0.0001)	4.89 (0.0190)	-0.50 (0.0001)	-1.15	-4	-7.19	-25
Mortality (per 100,000 registered patients)	Prescribed antibiotics	2.64 (<0.0001)	-0.013 (<0.0001)	0.46 (0.0124)	-0.054 (<0.0001)	-0.19	-7	-0.83	-33
	Not prescribed antibiotics	2.42 (<0.0001)	-0.007 (<0.0001)	0.53 (<0.0001)	-0.074 (<0.0001)	-0.36	-14	-1.24	-51
Mortality (per 1,000 RTI episode)	Prescribed antibiotics	1.87 (<0.0001)	-0.00035 (0.6302)	0.27 (0.0001)	-0.028 (<0.0001)	-0.06	-3	-0.39	-21
	Not prescribed antibiotics	1.86 (<0.0001)	-0.0023 (<0.0390)	0.19 (0.0590)	-0.037 (<0.0001)	-0.26	-16	-0.70	-43
Mortality rates, based on ICD-10 code (per 100,000 registered patients)		2.71 (<0.0001)	-0.016 (<0.0001)	0.67 (0.0084)	-0.08 (<0.0001)	-0.28	-11	-1.24	-53
Subgroup analyses:									
Mortality in the elderly age category (per 100,000 registered patients)		32.26 (<0.0001)	-0.18 (<0.0001)	8.86 (<0.0001)	-0.87 (<0.0001)	-1.52	-5	-11.90	-38

Figure 5-18 Interrupted time series analyses of all-cause mortality within 30-day follow-up following an uncomplicated RTI (per 100,000 registered patients), and with potential anomalies omitted, in England, April 2011 to March 2017



Similarly, findings based on mortality rates calculated using the denominator of RTI episodes demonstrated slight changes related to the QP; an increase in the level change (0.38 per 1,000 RTI episode) and a decrease in the post-QP trend (0.052 per 1,000 RTI episodes) (Table 5-10, Figure 5-19).

Figure 5-19. Interrupted time series analysis of all-cause mortality within 30-day follow-up (per 1,000 RTI episodes), April 2011 to March 2017

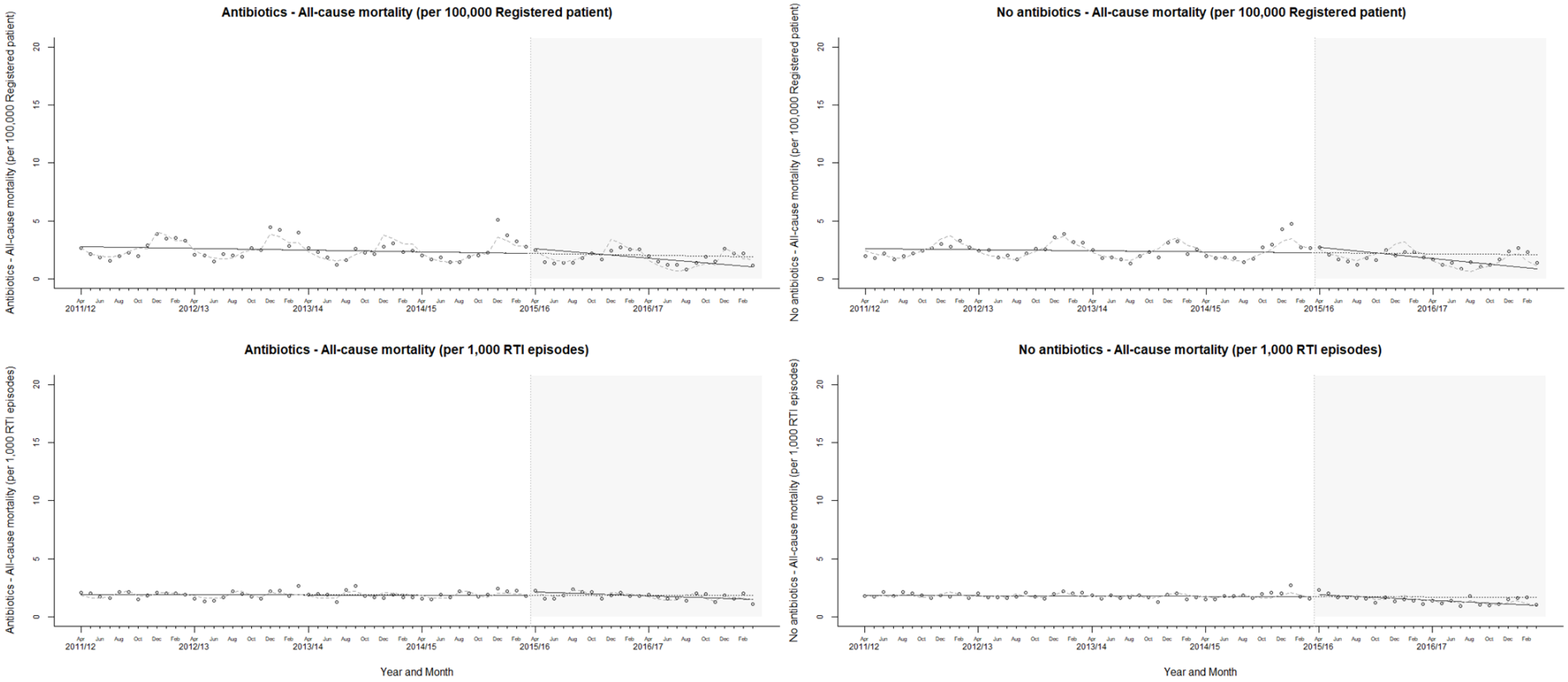


5.6.3 Sensitivity analysis

Analysis of antibiotic prescribing

Analysis of mortality (within 30-days of an initial RTI consultation) by whether patients were prescribed antibiotics or not, demonstrated that patients who received antibiotic prescriptions had a marginally higher mortality rate. Although the slope of mortality was decreasing to a slightly larger degree pre-QP in patients prescribed antibiotics, in that there was no real difference between mortality rates for those prescribed or not when the QP was introduced ($p<0.05$) (Table 5-10, Figure 5-20). Correlating with the QP, there was a slight level increase accompanied by a larger decrease in the mortality trend for patients prescribed compared to those not prescribed antibiotics. A year after the QP, the average monthly mortality rate was less than what would have been expected had the QP not been implemented, for those prescribed antibiotics as well as those who were not. For patients who had consulted and were at risk of a complication, this decline represented a 3% and 15% decrease relative to what would have been expected based on the counterfactual trend, for those who were prescribed antibiotics and those who were not, respectively i.e. greater decrease in mortality in those who were not prescribed antibiotics.

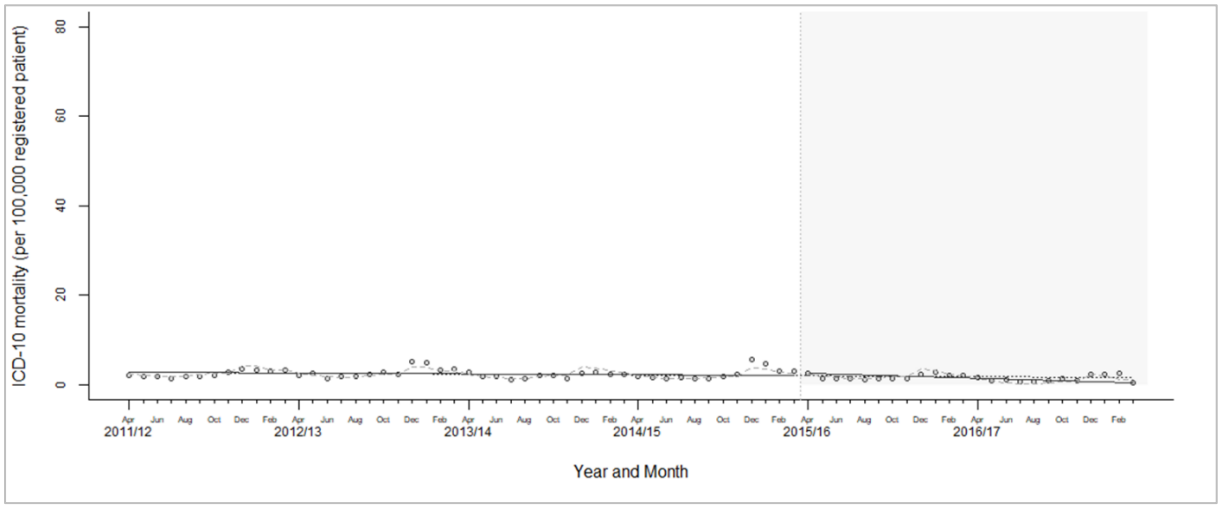
Figure 5-20. Sensitivity analysis: ITSA of mortality within 30-day in England, April 2011 to March 2017, by patients who were prescribed antibiotics or not at index RTI consultation, calculated as registered patient and RTI episode rates



Analysis of mortality for patients with an ICD-10 code for complication

Registered deaths which were coded with ICD-10 codes related to RTI complications were assessed to identify whether mortality related to the specific outcomes of interest demonstrated different trends compared to all-cause mortality. The exhibited trend was similar to that for all-cause mortality, in that the pre-QP trend was also decreasing prior to the QP, and there was a significant level increase (although this was a smaller increase of 0.67 per 100,000 patients) and a decrease in the post-intervention trend (although this was a smaller decrease of 0.08 per 100,000 patients) which coincided with the introduction of the QP (Table 5-10, Figure 5-21). This resulted in a similar 11% relative change 12 months post-intervention.

Figure 5-21. Interrupted time series analysis of the mortalities coded as ICD-10 complications within 30-day follow-up in England (per 100,000 registered patients), April 2011 to March 2017



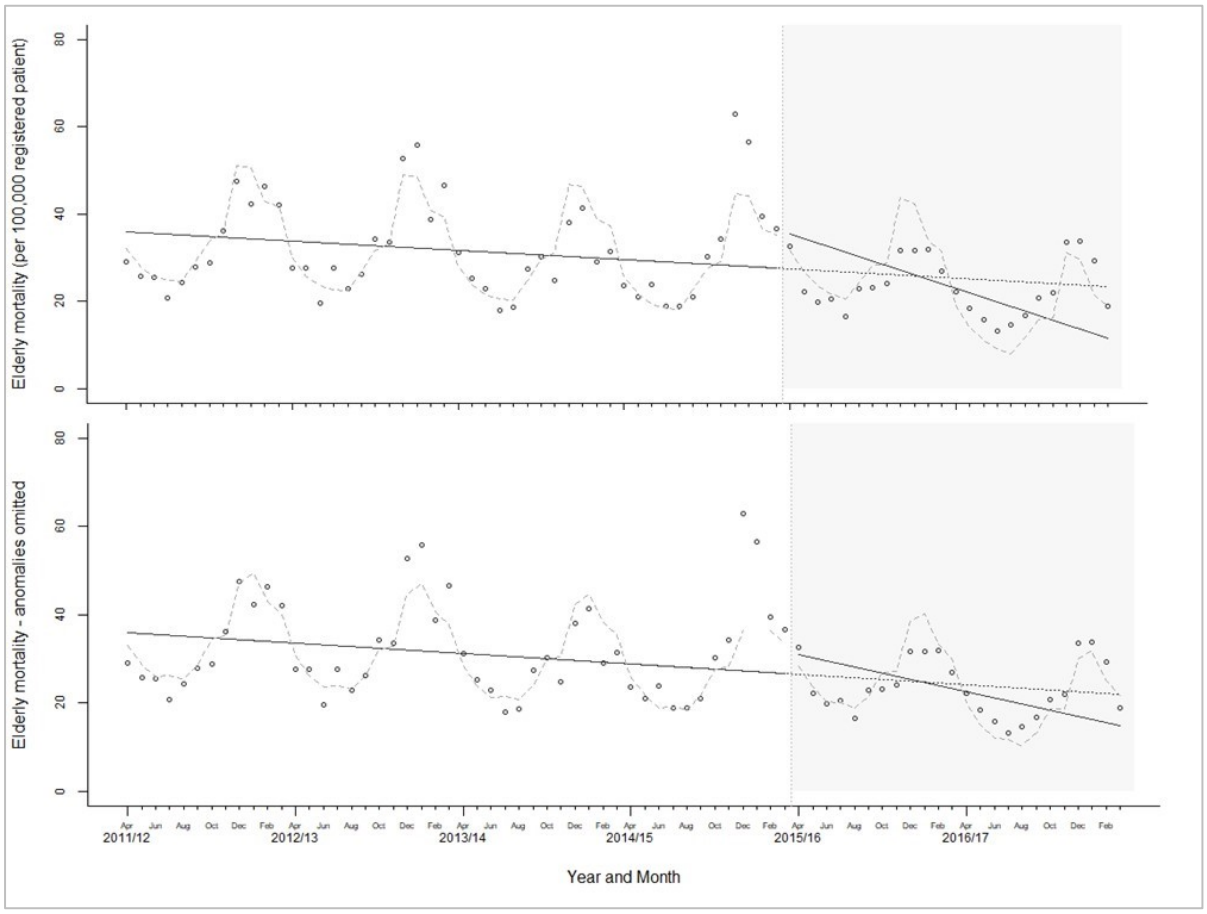
5.6.4 Subgroup analysis by age group: The elderly

As mortality was more prominent in the elderly, ITSA was only undertaken for this age group. All-cause mortality within 30-days of an RTI had been decreasing prior to the QP (by 0.18 per 100,000 registered patients, $p<0.05$). This slope reduced to a greater extent than observed for the main analysis post-QP (by 0.87 deaths per 100,000 patients). There was, however, a significant level increase in mortality

coinciding with the introduction of the QP (an increase of 8.86 deaths per 100,000 patients, $p<0.05$). This change, however, equated to a smaller 5% relative decrease 12 months post-QP (Table 5-10).

An ITSA which omitted December 2014 and January 2015 outliers reduced the level change to 4.89 deaths per 100,000 registered patients, and the relative change to 4% at 12 months post-QP (Table 5-10, Figure 5-22).

Figure 5-22. Interrupted time series analyses of all-cause mortality in the elderly within 30-day follow-up (per 100,000 registered patients), and with potential anomalies omitted, April 2011 to March 2017



5.7 Discussion

5.7.1 Summary of main findings

This is the first research to provide detailed national-level examination of the correlated impact of the QP, a national antimicrobial stewardship scheme, in terms of unintended consequences among patients with RTIs. The methodology used and findings are highly pertinent to policy makers, health planners and researchers in England and other countries with similar demographics.

Re-consultations

RTI consultation rates in primary care for RTIs decreased between April 2011 to March 2017. With fewer consultations for common infections, this concurrently led to fewer infectious episodes and subsequent fewer re-consultations.

Re-consultation rates for RTIs in primary care decreased over the 6-year study period from 45.91 per 1,000 registered patients to 30.98 per 1000 registered patients, with children and the elderly re-consulting the most often. Further decreases in the level and trend for re-consultations for RTIs, particularly for children, were associated with the introduction of the QP, although these were not statistically significant. This reduction in subsequent re-consultations may be related to GPs being able to devote more time to patients presenting at the index consultation, for indications such as severe respiratory infections and on appropriate antibiotic prescribing.[3] Patients who consulted with lower RTIs re-consulted more often than patients whose index consultation was for AOM, rhinosinusitis, sore throats, upper RTIs and viral respiratory infections. Lower RTIs, such as acute cough or acute bronchitis, are often clinically more severe, symptoms are more problematic and take a longer duration to resolve, and in such instances antibiotic prescribing may be advisable to prevent subsequent complications. Hence it would be expected that patients initially consulting with a lower RTI are likely to re-consult more often than patients with less severe upper RTIs.[179]

Routine vaccinations for seasonal influenza and pneumococcal disease, introduced in 2000 and 2003 respectively, reduced index RTIs and may have had implications on subsequent re-consultations. With an increased uptake of the influenza vaccine (from 65% in 2000 to 71-75% since 2003) and coverage of the pneumococcal vaccination (PPV23) (from 29% for over 65 year olds in 2003 to 70.5% in 2011) the rate of RTIs and subsequent re-consultations would be expected to also reduce.[202]

Primary care

Primary care consultations for what is regarded as complications of RTIs were shown to be on a gradual rise across the study period. The introduction of the QP in April 2014 was accompanied by a significant level drop in the rate of complications reported in primary care (1.04 per 100,000 registered patients). This drop may, to an extent, be explained by increases in the outliers seen in the winter of 2014/15, which may have elevated the trends seen prior to introduction of the QP. Alternatively, the reductions may be in line with the second measure of the QP, which aimed to reduce hospital admissions for adults and children with lower RTIs (discussed in Chapter 1). This measure, which along with its potential impact on hospital outcomes, may have impacted on the management of infections and complications in primary care.[64] The rate of complications assessed by RTI episodes, showed that for patients who consulted in primary care there was an overall increase post-QP in complications, although this was not statistically significant. Further analysis where the data were stratified by antibiotic prescribing suggested that there was a correlated increase in the level of complications for both patients prescribed antibiotics and those who were not, and that increases in complications were not related to changes in antibiotic prescribing.

The most common RTI complications reported in primary care were pneumonia and scarlet fever. Pneumonia showed a 4% relative increase 12-months post-QP. Increases were also seen in LRTI re-consultations and community-acquired pneumonia despite the increase in influenza and pneumococcal vaccine coverage, mentioned above, this may reflect limited effectiveness of the PPV23 pneumococcal vaccine among the older individuals (65 years and above).[202]

Where patients re-consult with an unresolved lower RTI, there may be added pressure for a general practitioner to prescribe antibiotics, which could lead to the overestimation and misclassification of pneumonia reported in primary care, if practitioners record a diagnosis of pneumonia to justify their decision to prescribe anitbiotics.[246] This would however impact data throughout the trend/study duration and would not necessarily impact on the incidence of pneumonia complication specifically after the introduction of the QP. Furthermore, a decision to record a condition as pneumonia to justify antibiotic prescribing is unlikely to be made lightly, as pneumonia is a serious complication.[133] Increasing pneumonia reports in the community have been reported in several studies, with a predominant burden in the elderly, as was also demonstrated in this research. This was thought to be in relation to the elderly having an increased prevalence of co-existing disease and comorbidities making them more prone to severe disease, and with an aging population a growth in these predisposing comorbidties.[202, 246-248] However, the literature also suggests that increases in pneumonia are not entirely attributed to aging populations and their co-morbidities, but possibly due to change in management of chest infection codes leading to an increase in pneumonia incidence,.[246, 248] There is a level of diagnostic uncertainty associated with primary care data as coding is often decided in relation to symptoms rather than disease categorisation, with certain research reporting the phenomenon of “code drifting”, particularly with the elderly population.[246] There is also diagnostic uncertainty within primary care as diagnostic investigations (radiological and bacteriological tests) are generally not performed in this setting in the UK.[246] Furthermore, although findings are corroborated by the literature, the pneumonia rates calculated may overestimate the burden in primary care by including patients who acquired pneumonia from the hospital setting. Increased pressure in the hospital setting to discharge patients has resulted in early discharge for patients with pneumonia, which may subsequently see patients seeking further management at their general practice.[248] Notably, there was not an increase in severity of pneumonia cases correlated with the QP, as there was a decrease in pneumonia hospital admissions and 30-day all-cause mortality, as discussed further below, which supports this theory.

Scarlet fever is a common childhood infection caused by *Streptococcus pyogenes* (also known as group A Streptococcus [GAS]). This bacterium may be found on the skin, throat and other sites of the body where it can colonise without causing harm. In certain instances, GAS can cause non-invasive infections such scarlet fever.[249] Following marked decreases in scarlet fever in England in the early 2000s, there was an unusual three-fold surge in incidence between 2013 and 2014 from 8.2 to 27.2 per 100,000 population, with this high incidence continuing every year since, but with a particular cyclic seasonal pattern between December to May (with peaks in March or April).[185, 249] This increase has been reported to mainly affect patients between two and eight years of age (median age of 4).[249] These published findings of scarlet fever outbreaks corroborate the findings seen here, in that, Scarlet fever was a complication prominent in the young, children 8 years and under in particular. There was a considerable rise in scarlet fever between January and March since 2014, however the same quarter in 2016/17 (post-QP) did not exceed the previous two peaks. There was a decline post-QP in the level and slope of scarlet fever within 30-days of an index RTI reported in primary care in children (p>0.05). Hence, the QP and national reductions in antibiotic prescribing have not seemingly been associated with unintended consequences or increasing the trends seen.

Scarlet fever hospital admissions were not assessed separately due to small counts, however recent literature suggest that scarlet fever hospital admissions, although unrelated to any index consultations in primary care or to an initial RTI, had also decreased corresponding to the introduction of the QP, although this may have been in relation to incomplete data.[91]

Secondary care

There was a reduction in hospital admissions for complications, subsequent to an RTI in primary care, coinciding with the QP (level decrease of 0.083 per 100,000 registered patients, p<0.05), which was seen across all age groups. The greatest reductions related to the QP, were reported in the elderly. Findings from the literature suggest that upper RTIs are more common amongst the young, whereas

lower RTIs are more frequent among adults and the elderly.[250] It would therefore be expected that the occurrence of complications would be higher amongst the adult and elderly age categories.

Where trends were assessed taking into account antibiotic prescribing at the index RTI consultation, there was no real difference between the changes in complications seen between patients who were prescribed antibiotics compared to those who were not. Where increases in hospital admissions were reported, these were for patients who were prescribed antibiotics rather than those who were not (based on episode rates), hence unrelated to changes in prescribing behaviour and the QP but indicative of a change in infections/infection severity in the community.

Assessment of the outcomes, where possible, revealed a potential increase in the BSI trend related to the QP and a decrease in hospital admissions for pneumonia, although these findings were not statistically significant. Notably, a national financially incentivised Commission for Quality and Innovation (CQUIN) scheme was simultaneously introduced in March 2015. This scheme set guidance and incentivised hospitals to improve early identification and treatment of sepsis.[251] This upsurge in screening for sepsis may be the basis for the increase in BSI reporting seen, which although correlated to the introduction of the QP, could be in relation to the CQUIN. Moreover, clinical coding standards were updated in October 2016, to recommend recording sepsis as the principal diagnosis in the coding sequence, i.e. sepsis should now be assigned as the primary code.[189, 252, 253] This change in coding and classification may have accounted to some extent for the reported increases in BSIs, although the main analysis had taken coding changes into account and used the hospital first episode list of codes combined. In addition, the sensitivity analysis which assessed primary ICD-10 codes only revealed a smaller change and decrease in hospital admissions for complications.

Mortality

All-cause mortality within 30-days of an RTI consultation in primary care demonstrated a level increase correlating with the QP, and a subsequent trend decrease in rates, resulting in 0.81 per 100,000

registered patients' deaths less than would have been expected 12 months post-QP. Mortality was most prominent within the elderly and exhibited similar changes in trend and level. Mortality trends and the correlated impact of the QP were similar for patients who had been prescribed antibiotics and those who had not, with patients who had been prescribed antibiotics demonstrating a 3% decrease in mortality 12 months after the QP, compared to a 15% decrease, relative to what would have been expected had the pre-QP trend continued (based on the underlying episode data).

Interpretation of the findings where the outcomes were extremely rare and where the counts per month were low (i.e. the decline in elderly hospital admissions, the incline in BSI admissions, the initial level increase and subsequent decline in morality in the elderly), makes conclusions about changes in such small numbers extremely difficult. The initial increase in mortality correlated with the introduction of the QP, and the high mortality in 2014/15, could be associated with the lower than average influenza vaccine effectiveness in 2014/15, with estimates of the effectiveness of the adult flu vaccines used in the UK being approximately 34%, and a lower estimate reported mid-season at 3% (effectiveness usually ranges between 25 to 70%).[202, 254] The poor performance of the 2014/15 influenza vaccine was attributed to a mismatch between the vaccine strain and the circulating influenza strain.[254, 255] The literature suggests that the ineffectiveness of the 2014 influenza vaccine resulted in the number of excess deaths being one-third higher than average in the winter period.[228] Where the effectiveness of the vaccine is low, patients can develop co/secondary bacterial infections, resulting in severe illness requiring hospitalisation (such as pneumonia; although hospital admissions for pneumonia did not depict a level increase as has been seen with mortality), or there may be a subsequent impact on deaths amongst at-risk groups, such as the elderly.[255-257] Furthermore, reports in 2015 suggest that there was an increase in influenza outbreaks in care homes, which led to an increase in hospital admissions and a rise in deaths in the elderly.[254]

5.7.2 Findings in relation to other published evidence

The findings from this chapter are in line with published studies which assessed interventions and adverse outcomes. A recent study which assessed the QP in England and adverse outcomes unrelated to index uncomplicated respiratory indications seen in primary care, found no association between the QP and adverse clinical outcomes in primary or secondary care.[91] Other studies which assessed antimicrobial stewardship programmes (educational and guidelines), without the use of financial incentives, showed similar findings. A practice-based randomised controlled trial conducted in Wales assessed the association between a multifaceted educational programme and re-consultation rates as well as hospital admissions for RTIs, and found no significant difference between practices which received the educational programme compared to those which did not.[142] Similarly, a study undertaken in Italy, assessing the potential impact of paediatric guidelines for the treatment of AOM, found no significant associations with the cases of mastoiditis.[149] A study in Sweden which assessed the introduction of new guidelines for diagnosis and treatment of AOM, although reporting significant decreases in antibiotic prescribing, did not find this increased the incidence of mastoiditis.[145] A research abstract published in Scotland found no association between an AMS programme (which had an accompanied reduction in population antibiotic exposure) and hospital admissions for peritonsillar abscess, mastoiditis and community-acquired pneumonia.[258]

5.7.3 Strengths and limitations

The research has many strengths, being a large population-based study linking primary care data to large population-level hospital admissions and mortality data to identify changes in rare outcomes. The studies used extracted national data for over two million patients and approximately 5.5 million episodes of RTIs between April 2011 and March 2017.

The use of an ITS, a strong quasi-experimental design, to assess associations between the QP and unintended consequences is particularly useful where the intervention of interest has already been

implemented and where a randomised controlled trial would not be feasible. Segmented regression permits statistical analyses of changes in the level and trend of outcomes, whilst addressing threats to internal validity. This method, however, does not provide causal evidence for the outcomes assessed, and other interventions over the study period, particularly pertaining to the same period as that of the QP (April 2015), may have also influenced the trend and changes observed (including the CQUIN intervention mentioned earlier).

A limitation which needs to be considered when interpreting these findings is that although the study population was extremely large, the outcomes (complications of RTIs) assessed were rare and the numbers were very small. Where variations in these rare outcomes occurred, the relative changes could appear more substantial then they potentially are, i.e. a small absolute change in a rare outcome may result in a large percentage change. It is important to measure impact on unintended consequences however as these are preventable and would be costly to the individual in terms of morbidity and potentially mortality, as well as economically to the NHS.

Another limitation worth acknowledging is the difficulty in defining certain complications accurately. Pneumonia, which is often diagnosed using x-rays, is difficult to distinguish in general practice, which may have led to misclassification of some pneumonia being categorised as lower RTIs, and vice versa.[202] Defining prior hospital admissions/healthcare interactions for cases of pneumonia reported in primary care would permit better understanding of the trends seen by removing cases unrelated to primary care. The literature suggests changes in healthcare provision with increased pressure for early discharge from hospitals, which could lead to those patients subsequently seeking further attention in primary care i.e. misclassification of hospital-acquired pneumonia as community-acquire pneumonia in primary care.[248]

Furthermore, defining community-acquired pneumonia in secondary care could have been improved by having a more stringent criterion. The methods used did attempt to distinguish community-acquire infections by not including outcomes where the patient had a recorded hospital admission within the

RTI 30-day infectious episode, prior to the complication. Published research, however, often uses a 14-day exclusion period after any hospitalisation to define community-acquired pneumonia.[186, 202] Furthermore, the use of an infection episode of 30-days may have excluded patient outcomes that were diagnosed after this period. Certain outcomes such as sepsis may occur up to 60-days post initial index RTI, and it may therefore be possible that a few outcomes were omitted from the analysis.

5.7.4 Conclusions

Findings from this chapter have implications for healthcare practice beyond England and would benefit other countries in terms their antimicrobial stewardship programmes. Reducing inappropriate antibiotic prescribing in order to try and reduce the rate of AMR has been recognised worldwide. The results associated with the introduction of the QP, and reductions in antibiotic prescribing in England, have had no significantly associated negative health impacts on patients who consult in general practice with uncomplicated RTIs, and suggest no significant consequences on patient outcomes, with the exception of a few findings such as increased mortality in the elderly which were not sustained. Caution must be taken when interpreting results from this chapter, as the data were aggregated from across England and can't be used to ascertain cause and effect. Furthermore, the findings are based on rare outcomes and in instances small counts.

5.7.5 Recommendations and implications for practice or research

Future research into the effects of controlling antibiotic prescribing on RTI complications and outcomes could be focused on patients who are at higher risk of unintended consequences (i.e. elderly) is required. Findings in this chapter suggest that forthcoming initiatives may benefit from targeting interventions at particular age groups or risk groups. Furthermore, research suggests the incidence of lower RTIs and community acquired pneumonia increased with increasing deprivation.[202] Assessment

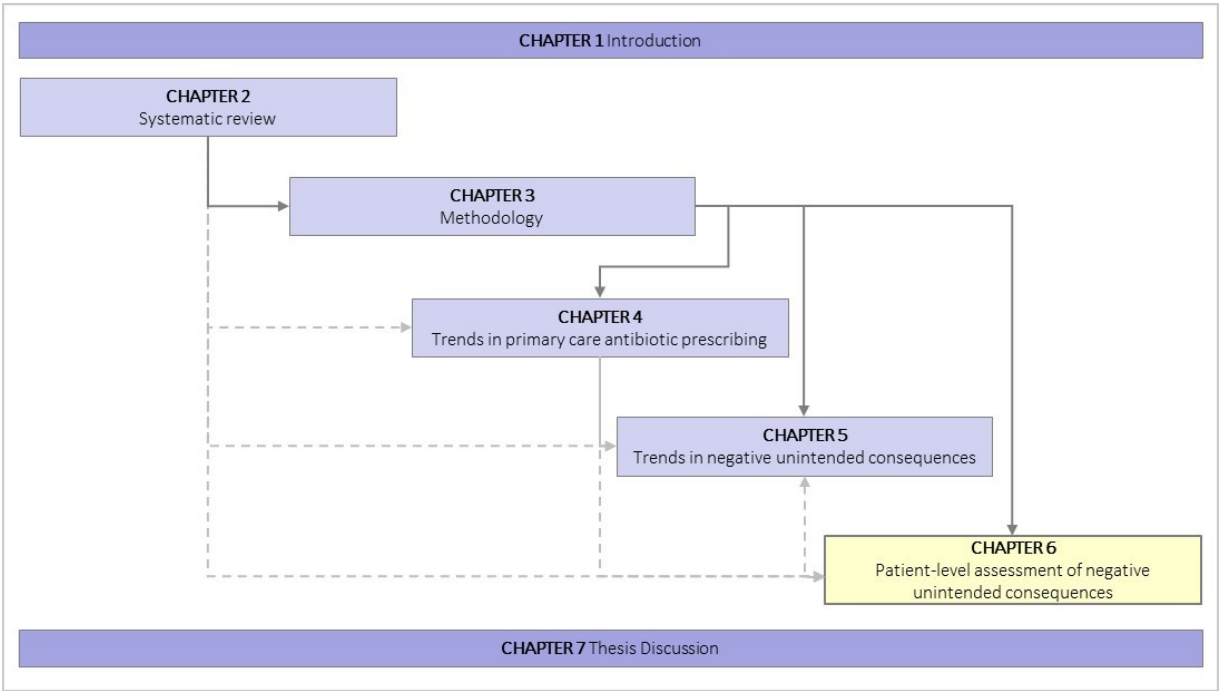
of unintended complications by region (within England) and deprivation may further enhance knowledge and understanding of risk groups.

Further work assessing the healthcare pathways combined would be beneficial. In that complications and outcomes are not assessed by setting but within the same respiratory infectious episode; a patient is recorded as having a complication within 30-days if there is an outcome reported within linked primary care, secondary care or is reported as having died. In this way, the healthcare of a patient as a whole entity would be investigated rather than as segregated interactions. This would permit investigation of whether reductions in hospital admissions were related to increases in mortality. The methods used within this chapter enabled the measurement of the potential impact by setting and is useful when identifying any impact on health services and systems. Not linking throughout also enabled the assessment of complications by severity and maintained the larger sample size when assessing primary care outcomes, preserving power and generalisability of the findings.

Research on patient-level impact of the QP and patient-level antibiotic prescribing and complications, rather than focusing on aggregated data, could be beneficial in providing further support to the findings. This has been undertaken in the subsequent chapter (Chapter 6). Alternatively, using a control population, such as Wales, Scotland or Northern Ireland, where the QP was not implemented would prove useful comparisons.

Regular repetition of this research or the creation of surveillance of unintended consequences could be implemented to monitor further reductions or changes in antibiotic prescribing, the impact of future national interventions, provide an early identification of emerging unintended harm, and provide reassurance and guidance to clinicians, policy makers and the public. This would be particularly useful to understand the impact of subsequent updates of the QP such as the 2016/17 guidance which specified the intention to reduce the number of antibiotic prescribing in primary care by 4% or to the England 2013/14 mean value.[65]

CHAPTER 6



Summary:

This chapter made use of linked data sources to identify unintended consequences across healthcare settings for the same RTI episode (within 30-days), i.e. follows a patients' care pathways and combined complications. The linked data was used to investigate whether patients had an increased likelihood of complications correlated with the introduction of the QP. The unit of analysis was patient-level, rather than ecological, and multivariable analyses were undertaken. The findings suggest that the odds of a complication may have slightly increased post QP compared to the odds pre-QP, however, complications were shown to have been on a gradual increasing trend in Chapter 5. Findings corroborate reports in Chapter 5, in that, the likelihood of antibiotic prescribing post-QP was less than pre-QP, and there were greater odds of complications post-QP in patients who had been prescribed antibiotics compared to those who had not.

6 ASSESSMENT OF POTENTIAL NEGATIVE UNINTENDED CONSEQUENCES USING PATIENT-LEVEL DATA

6.1 Patient-level analysis of the occurrence of unintended consequences for index uncomplicated respiratory tract infections

The previous chapter outlined the ecological association between the introduction of the QP 2015/16 and the aggregated occurrence of unintended consequences. This chapter expands on previous findings by further utilising patient-level data to determine whether after accounting for patient and general practice characteristics the introduction of the QP was associated with increased complications.

The potential positive impact of antibiotic prescribing on preventing RTI complications is not a novel concept,[259] however related published literature of high quality is lacking (Chapter 2). Studies of RTIs, which are predominantly self-limiting infections, reported a correlation between antibiotic use and patients being less likely to develop complications (Chapter 2). Several studies, however, lacked an adequate sample size to assess rare outcomes and often had not been designed to primarily assess complications. The research reported here has the advantage of having a large sample size, and assessing an intervention, namely the QP 2015/16, rather than antibiotic prescribing, to identify any implications this may have had on complications across healthcare settings. Hierarchical multivariable logistic modelling was employed as this uses unaggregated individual patient-level data and does not pertain to the ecological fallacy (see section 2.5.2) to the same degree as the TSA used in the previous chapters.

6.1.1 Hypothesis

As in Chapter 5, the hypothesis is that subsequent to the introduction of the QP there have been suboptimal reductions in antibiotic prescribing in primary care for uncomplicated RTIs, which has resulted in increased complications, detected via primary care, secondary care or mortality data.

This research follows a patients' care pathway within a 30-day RTI episode and takes a different approach to the analyses undertaken in Chapter 5 in that unintended consequences are identified across healthcare settings for the same RTI episode.

6.2 Method

6.2.1 Study population and outcome of interest

The data sources used (CPRD, HES and ONS mortality data) and their linkage has been outlined in Chapter 3. The study population included all CPRD "acceptable" patients with a permanent registration status (i.e. excluded temporary residents and visitors), who had not 'opted out' from providing data in up-to-standard participating English general practices, and who were registered at general practices eligible for HES and ONS linkage (Chapter 3). Patient records were included if they had had an index consultation at a general practice for an uncomplicated RTI within the study period of March 2013 to April 2017 (two years pre- and two years post-QP). Thirty-day RTI episodes were created and any CPRD consultations within the 30-days were removed as they were assumed to be related to the index consultation and not a new episode of infection. The outcome of interest was the development of a more severe infection described as a "complication" (Chapter 3, with code lists in Appendix 19). The occurrence of a complication was assessed across all three data sources and across healthcare settings, i.e. a patient was classified as having a complication where within 30 days they consulted in primary care with a more severe infection (CPRD), or had a hospital admission (HES) for a complication (with no previous hospital discharge within 14 days of hospital admission), or had died (ONS mortality data).

6.3.2 Sample size calculation

The published literature suggests that 1.4% (0.0137) of patients develop complications (quinsy, sinusitis, otitis media, cellulitis or impetigo).[129] To detect a clinically significant increase of 10% in complications (0.0151) following a decrease in antibiotic prescribing, a total of 286,696 patients (143,348 in both the pre-QP group and the post-QP group) would be required (2 sided α=0.025 (Bonferroni correction), β=0.80).

6.2.2 Statistical methods

Complications were aggregated within an RTI episode (of 30 days) to produce a binary outcome variable (i.e. identifying whether one complication [reported in primary care, hospital admissions or mortality records] had occurred or not within that RTI episode). A variable was created to differentiate the time period the data pertained to, i.e. the 4-year time period was categorised into 2-years, pre- and 2-years post QP. For ease of interpretation (and for the purpose of testing interactions) certain covariates were categorised: age was categorised (as children [1-15 years], adults [16-64 years] and elderly [65 years and over]), general practice registered patients, and general practice RTI consultations were categorised into quintiles (with quintile 5 being the general practices with the greatest registered patient counts and the general practices with the greatest RTI index consultations).

Univariate and multivariable logistic regression models were used to determine whether the QP had unintended consequences as measured by whether there were increased odds of complications pre- compared to post-QP. To build the statistical models, probable risk factors thought to be associated with both the exposure and the outcome were determined *a priori*. The predetermined risk factors assessed were informed by the systematic literature review completed in Chapter 2, as well as discussions with a practicing clinician and statistician, and included: age category, sex, patient antibiotic prescription on the index RTI consultation date, general practice registered patients

(quintile), and general practice uncomplicated RTI consultations (quintile). All these factors were binary or categorical variables and included hierarchical data.

Following univariate analysis (which provided assessment of crude Odds Ratios ([OR]), the final adjusted models were three-level mixed-effects logistic regression models (patients with RTI episodes who were nested within general practices, who were nested within regions. Chapter 3 contains further details, Figure 3-6). The multivariable hierarchical logistical regression model built used a stepwise selection process, assessing the fit of each model by comparing it to simpler models (i.e. removing explanatory variables and testing fit) using likelihood ratio (LHR) tests, followed by assessing the use of interaction terms, and finally including assessment of clusters. Interactions were assessed within the models between the exposure variable (QP year [the variable which identified pre- and post-QP time periods]) and antimicrobial prescribing, the exposure and age category, and between exposure and RTI consultations within general practices. Assessing potential interactions, or effect modifiers, was undertaken to determine whether different age groups, antibiotic prescribing, or the volume (quintile) of RTI consultations in a given general practice influenced the effect of the exposure on the outcome (i.e. complications).

To avoid collinearity, variables which were closely correlated (or were the same, i.e. age group 1 and age group 2 in univariate analysis) were assessed separately for inclusion, with the most significant retained. To test calibration (i.e. the model's ability to predict accurately) the Hosmer-Lemeshow goodness-of-fit test and ROC curves were used.[260 261]

6.2.3 Sensitivity analysis

A multivariable logistic model was also developed separately for patients who were and were not prescribed antibiotics, to identify whether the outcome of complications was independent of the QP. This alternate method should supplement the analyses in identifying unintended consequences of the QP 2015/16.

6.3 Results

6.3.1 Patient characteristics

There were 1,450,935 CPRD patients (registered in 405 general practices across the 10 regions in England) who had consulted for an uncomplicated RTI and had a 30 day infection episode created, between April 2013 to March 2017 (pre-QP period: n= 1,141,290 patients, post-QP period: n= 639,537) whose records were eligible for HES and ONS linkage. These patients accounted for the total of 2,965,902 RTI episodes assessed (2,952,847 of which did not progress into complications). Of these, there were 13,055 RTI episodes which progressed into what was defined as a complication (Pre-QP: 8,456, Post-QP: 4,599. Table 6-1); 6,740 reported within the CPRD data, 5,658 reported within the HES data (of which 985 [17.4%] had been captured within CPRD), 2,332 reported within the ONS data (of which 389 [16.7%] had been captured within CPRD, and further 301 captured within HES [12.9%]). Table 6-1 displays the distribution of complications across patient level factors of interest, including whether the patient had been prescribed antibiotics at the index RTI consultation of the episode, and whether the complication had occurred pre- or post-QP. The patient characteristics table (as well as the univariate analysis) suggests that patients who developed complications were more likely to be of older age, males, been prescribe antibiotics at the index RTI consultation, registered within larger general practices, where the general practices had the greatest RTI consultations, and where patients had an RTI episode in the North East of England. The patient characteristics variables were further assessed in univariate and multivariable analyses discussed below.

Table 6-1. Characteristics of included patients with a 30-day RTI episode in England, between April 2014 and March 2017

Variable	No complications n= 2,952,847 (99.56%)	Complications n= 13,055 (0.44%)	Total n= 2,965,902	*P* value
Treatment group				0.0237
Pre-QP period	1,940,497 (99.57%)	8,456 (0.43%)	1,948,953	
Post-QP period	1,012,350 (99.55%)	4,599 (0.45%)	1,016,494	
Mean age (SD)	36.17 (SD: 27.13)	60.49 (SD: 29.56)	36.27 (SD: 27.19)	<0.0001
Age category 1 (years)				<0.0001
0-4	528,276 (99.80%)	1,043 (0.20%)	529,319	
5-15	416,968 (99.82%)	764 (0.18%)	417,732	
16-24	232,358 (99.81%)	437 (0.19%)	232,795	
25-34	280,237 (99.79%)	582 (0.21)	280,819	
35-44	298,978 (99.76%)	720 (0.24)	299,698	
45-54	319,115 (99.74%)	837 (0.26%)	319,952	
55-64	299,830 (99.63%)	1,115 (0.37%)	300,945	
65-74	293,593 (99.39%)	1,811 (0.61%)	295,404	
75-84	195,230 (98.70%)	2,574 (1.30%)	197,804	
85 and over	88,262 (96.53%)	3,172 (3.47%)	91,434	
Age category 2 (years)				<0.0001
Children (0-15)	945,244 (99.81%)	1,807 (0.19%)	947,051	
Adults (16-64)	1,430,518 (99.74%)	3,691 (0.26%)	1,434,209	
Elderly (65 and over)	577,085 (98.71%)	7,557 (1.29%)	585,642	
Sex				<0.0001
Male	1,252,308 (99.51%)	6,132 (0.49%)	1,258,440	
Female	1,700,539 (99.59%)	6,923 (0.41%)	1,707,462	
Antibiotics at index RTI consultation				<0.0001
No	1,554,968 (99.60%)	6,323 (0.40%)	1,561,291	
Yes	1,397,879 (99.52%)	6,732 (0.48%)	1,404,611	
GP practice registered patients				<0.0001
Quintile 1 (lowest reg pt. counts)	591,131 (99.59%)	2,410 (0.41%)	593,541	
Quintile 2	592,534 (99.56%)	2,601 (0.44%)	595,135	
Quintile 3	588,949 (99.56%)	2,627 (0.44%)	591,576	
Quintile 4	592,512 (99.56%)	2,599 (0.44%)	595,111	
Quintile 5 (highest reg pt. counts)	587,721 (99.52%)	2,818 (0.48%)	590,539	
GP practice RTI consultations				<0.0001
Quintile 1 (lowest RTI consultations)	591,277 (99.61%)	2,342 (0.39%)	593,619	
Quintile 2	591,339 (99.54%)	2,761 (0.46%)	594,100	
Quintile 3	589,481 (99.59%)	2,425 (0.41%)	591,906	
Quintile 4	599,715 (99.57%)	2,595 (0.43%)	602,310	
Quintile 5 (highest RTI consultations)	581,035 (99.50%)	2,932 (0.50%)	583,967	
Region				<0.0001
North East	45,046 (99.27%)	325 (0.72%)	45,371	
North West	411,075 (99.56%)	1,834 (0.44%)	412,909	
Yorkshire and the Humber	46,729 (99.43%)	267 (0.57%)	46,996	
East Midlands	6,0.23 (99.32%)	41 (0.68%)	6,064	
West Midlands	415,151 (99.53%)	1,945 (0.47%)	417,096	
East of England	246,924 (99.52%)	1,180 (0.48%)	248,104	
South West	292,289 (99.41%)	1,730 (0.59%)	294,019	
South Central	479,062 (99.53%)	2,284 (0.47%)	481,346	
London	468,764 (99.69%)	1,451 (0.31%)	470,215	
South East Coast	541,784 (99.63%)	1,998 (0.37%)	543,782	

6.3.2 Findings from the logistic regression models investigating the effect of the QP 2015-16 on complications and antibiotic prescribing

The univariate analysis, which provides the associations of each risk factor with the outcome of complication (crude odds ratio, 95% confidence intervals and *p* values), can be seen in Table 6-2 and Table 6-3. Table 6-2 suggests that the crude odds of being prescribed an antibiotic at the index RTI consultation decreased, on average, by 14% for patients who consulted during the post-QP period compared to those pre-QP. The 95% confidence interval for this odds ratio is narrow and does not include the value of 1, suggesting that this is a significant intervention effect ($p<0.05$).

Table 6-3 shows that patients who consulted post-QP, on average, were 1.04 (crude OR) times more likely to develop a complication within 30-days compared to patients consulting with an RTI pre-QP ($p<0.05$). All the other independent variables assessed were also significantly associated with the dependent variable (the outcome of developing a complication within 30 days of an index RTI primary care consultation) and were assessed further in multivariable models. Importantly, the univariate analysis suggests an association between antibiotic prescribing and developing complications across the entire cohort (crude OR: 1.18 $p<0.05$) (i.e. regardless of the inclusion of the QP variable).

Table 6-2. Characteristics and univariate analysis investigating the effect on antibiotic prescribing, for patients with an RTI episode in England, between April 2014 and March 2017

Variable	**No antimicrobials n= 1,561,291**	**Antimicrobial n= 1,404,611**	**Total n= 2,965,902**
Treatment group			
Pre-QP period	1,000,922 (51,36%)	948,031 (48.64%)	1,948,953
Post-QP period	560,369 (55.10%)	456,580 (44.90%)	1,016,494

Variable	**Antibiotic prescribing at index RTI consultation**		
	Crude OR	**95% CI**	***P* value**
Treatment group			<0.0001
Pre-QP period	REF	REF	
Post-QP period	0.86	(0.85 - 0.86)	<0.001

Table 6-3. Univariate analysis investigating the effect of explanatory variables on RTI complications, for patients with an RTI episode in England, between April 2014 and March 2017

Variable	Complication event within 30 days		
	Crude OR	95% CI	*P* value
Treatment group			0.0237
Pre-QP period	REF	REF	
Post-QP period	1.04	(1.01 - 1.08)	0.023
Age category 1 (years)			<0.0001
0-4	REF	REF	
5-15	0.93	(0.85 - 1.02)	0.117
16-24	0.95	(0.85 - 1.07)	0.394
25-34	1.05	(0.95 - 1.16)	0.329
35-44	1.22	(1.11 - 1.34)	<0.001
45-54	1.33	(1.21 - 1.46)	<0.001
55-64	1.88	(1.73 - 2.05)	<0.001
65-74	3.12	(2.89 - 3.37)	<0.001
75-84	6.68	(6.21 - 7.18)	<0.001
85 and over	18.20	(16.97 - 19.53)	<0.001
Age category 2 (years)			<0.0001
Children (0-15)	REF	REF	
Adults (16-64)	1.35	(1.28 - 1.43)	<0.001
Elderly (65 and over)	6.85	(6.51 - 7.21)	<0.001
Sex			<0.0001
Male	REF	REF	
Female	0.83	(0.80 - 0.86)	<0.001
Antibiotics at index RTI consultation			<0.0001
No	REF	REF	
Yes	1.18	(1.14 - 1.23)	<0.001
General practice registered patients			<0.0001
Quintile 1 (lowest registered patient counts)	REF	REF	
Quintile 2	1.08	(1.02 - 1.14)	0.009
Quintile 3	1.09	(1.04 - 1.16)	0.001
Quintile 4	1.08	(1.02 - 1.14)	0.010
Quintile 5 (highest registered patient counts)	1.18	(1.11 - 1.24)	<0.001
General practice RTI consultations			<0.0001
Quintile 1 (lowest RTI consultations)	REF	REF	
Quintile 2	1.18	(1.12 -1.25)	<0.001
Quintile 3	1.04	(0.98 -1.10)	0.192
Quintile 4	1.09	(1.03 - 1.16)	0.002
Quintile 5 (highest RTI consultations)	1.27	(1.21 - 1.35)	<0.001
Region			<0.0001
North East	REF	REF	
North West	0.62	(0.55 - 0.70)	<0.001
Yorkshire and the Humber	0.79	(0.67 - 0.93)	0.005
East Midlands	0.94	(0.68 - 1.31)	0.727
West Midlands	0.65	(0.58 - 0.73)	<0.001
East of England	0.66	(0.59 - 0.75)	<0.001
South West	0.82	(0.73 - 0.92)	0.001
South Central	0.66	(0.59 - 0.74)	<0.001
London	0.43	(0.38 - 0.48)	<0.001
South East Coast	0.51	(0.45 - 0.58)	<0.001

Table 6-4 shows the results of the multivariable logistic regression model investigating the effect of the introduction of the QP on developing a complication within a 30-day RTI episode, adjusted for covariates (which were included following tests of goodness of fit and calibration). The interaction terms tested were not significant and were not included within the final model.

The main factor of interest was the treatment group, which referred to whether the patient's infection episode had occurred pre- or post-QP period. After adjustment for covariates, the odds of developing a complication was higher in patients who consulted with an RTI post-QP compared to pre-QP (p<0.05). The odds of a complication within 30 days of an index RTI increased, on average, by 8% (adjusted OR: 1.08 [95% CI: 1.04 - 1.12]) in the post-QP group in relation to the odds of the pre-QP group (Table 6-4). After further adjustment for clustering at general practice and region level (405 practices, 10 regions), the odds of complication were still higher in the post-QP group in relation to the pre-QP group with little change in the effect size and confidence intervals from the non-hierarchical model (OR: 1.07, p<0.05).

The hierarchical model suggests that when considering the adjusted factors, patients in the elderly category (the odds of complications in the elderly was 6.83 times the odds in children), males (18% greater odds in males compared to the odds of females, p<0.05), those who had been prescribed antibiotics at the index RTI consultation, those registered at larger practices (registered patients used as a proxy for this; quintile 5), and those practices with the highest volume of RTI consultations presented (quintile 5) had greater odds of developing complications, when time-period and all other variables are held constant.

Table 6-4. Multivariable adjusted analysis investigating the effect of the QP on RTI complications, for patients with an RTI episode in England, between April 2014 and March 2017

Variable	Complication event within 30 days (n= 2,965,902)					
	Adjusted OR	**95% CI**	***P* value**	**Adjusted OR multilevel model**	**95% CI**	***P* value**
Treatment group						
Pre-QP period	REF	REF		REF	REF	
Post-QP period	1.08	(1.04-1.12)	<0.001	1.07	(1.03 - 1.13)	0.001
Age category (years)						
Children (0-15)	REF	REF		REF	REF	
Adults (16-64)	1.37	(1.3 - 1.45)	<0.001	1.36	(1.28 - 1.44)	<0.001
Elderly (65 and over)	6.83	(6.49 - 7.2)	<0.001	6.71	(6.37 - 7.07)	<0.001
Sex						
Male	REF	REF		REF	REF	
Female	0.82	(0.8 - 0.85)	<0.001	0.82	(0.8 - 0.85)	<0.001
Antibiotics at index RTI consultation						
No	REF	REF		REF	REF	
Yes	1.04	(1.003 - 1.08)	0.035	1.09	(1.05 - 1.13)	<0.001
General practice registered patients						
Quintile 1 (lowest reg pt. counts)	REF	REF		REF	REF	
Quintile 2	1.09	(1.02 - 1.16)	0.008	1.14	(0.99 - 1.32)	0.064
Quintile 3	1.13	(1.06 - 1.22)	<0.001	1.24	(1.05 - 1.45)	0.009
Quintile 4	1.01	(0.94 - 1.09)	0.812	1.26	(1.06 - 1.49)	0.008
Quintile 5 (highest reg pt. counts)	1.06	(0.97 - 1.16)	0.186	1.30	(1.06 - 1.58)	0.010
General practice RTI consultations						
Quintile 1 (lowest RTI consultations)	REF	REF		REF	REF	
Quintile 2	1.18	(1.12 -1.26)	<0.001	1.10	(1.01 -1.2)	0.033
Quintile 3	1.01	(0.95 -1.09)	0.690	0.97	(0.88 -1.07)	0.555
Quintile 4	1.09	(1.02 - 1.18)	0.018	0.99	(0.88 - 1.11)	0.826
Quintile 5 (highest RTI consultations)	1.27	(1.17 - 1.39)	<0.001	1.06	(0.93 - 1.21)	0.381
Region						
North East	REF	REF				
North West	0.59	(0.52 - 0.66)	<0.001			
Yorkshire and the Humber	0.67	(0.57 - 0.79)	<0.001			
East Midlands	1.05	(0.75 - 1.46)	0.755			
West Midlands	0.60	(0.53 - 0.67)	<0.001			
East of England	0.66	(0.58 - 0.75)	<0.001			
South West	0.73	(0.65 - 0.83)	<0.001			
South Central	0.63	(0.56 - 0.71)	<0.001			
London	0.48	(0.43 - 0.55)	<0.001			
South East Coast	0.50	(0.44 - 0.56)	<0.001			

6.3.3 Findings from the sensitivity analysis: logistic regression models investigating the effect of the QP 2015-16 on complications for patients who were not prescribed antibiotic

To interrogate the findings further, the risk of complications was modelled separately for patients who had and those who had not been prescribed antibiotics at initial RTI consultation. The multilevel adjusted models found similar increases in odds, suggesting that the risk of complication was increased post-QP compared to pre-QP regardless of antibiotic use at initial RTI consultation (OR of complication pre- compared to post-QP for patients who were prescribed antibiotics: 1.09, $p<0.05$, and for patients who were not prescribed antibiotics: 1.07, $p<0.05$) (Table 6-5). Notably, the OR of developing complications pre- compared to post-QP was higher for patients who had been prescribed antibiotics than for those who had not.

Table 6-5. Sensitivity analysis: Multivariable adjusted analysis investigating the effect the effect of the QP on RTI complications, for patients with an RTI episode in England, between April 2014 and March 2017

Variable	Not prescribed antibiotics - Complication event within 30 days (n=1,561,291)						Prescribed antibiotics - Complication event within 30 days (n=1,404,611)					
	Adjusted OR	95% CI	*P* value	Adjusted OR & Multilevel model	95% CI	*P* value	Adjusted OR	95% CI	*P* value	Adjusted OR & Multilevel model	95% CI	*P* value
Treatment group												
Pre-QP period	REF	REF		REF	REF		REF	REF		REF	REF	
Post-QP period	1.06	(1.002 - 1.12)	0.042	1.07	(1.004 - 1.13)	0.036	1.11	(1.05 - 1.17)	<0.001	1.09	(1.03 - 1.16)	0.003
Age category (years)												
Children (0-15)	REF	REF		REF	REF		REF	REF		REF	REF	
Adults (16-64)	1.23	(1.14 - 1.33)	<0.001	1.23	(1.14 - 1.33)	<0.001	1.53	(1.4 - 1.67)	<0.001	1.52	(1.39 - 1.66)	<0.001
Elderly (65 and over)	7.04	(6.58 - 7.53)	<0.001	6.97	(6.51 - 7.46)	<0.001	6.73	(6.2 - 7.3)	<0.001	6.60	(6.08 - 7.17)	<0.001
Sex												
Male	REF	REF		REF	REF		REF			REF		
Female	0.83	(0.80 - 0.88)	<0.001	0.83	(0.80 - 0.88)	<0.001	0.83	(0.77 - 0.85)	<0.001	0.81	(0.77 - 0.85)	<0.001
GP practice registered patients												
Quintile 1 (lowest reg pt. counts)	REF	REF		REF	REF		REF	REF		REF	REF	
Quintile 2	1.11	(1.01 - 1.21)	0.023	1.14	(0.96 - 1.34)	0.133	1.07	(0.98 - 1.17)	0.125	1.17	(0.99 - 1.38)	0.063
Quintile 3	1.23	(1.11 - 1.36)	<0.001	1.24	(1.03 - 1.5)	0.021	1.05	(0.96 - 1.16)	0.298	1.18	(0.97 - 1.43)	0.093
Quintile 4	1.04	(0.94 - 1.16)	0.444	1.18	(0.97 - 1.44)	0.101	0.98	(0.89 - 1.09)	0.741	1.22	(0.99 - 1.49)	0.054
Quintile 5 (highest reg pt. counts)	1.05	(0.93 - 1.2)	0.444	1.17	(0.93 - 1.5)	0.184	1.07	(0.95 - 1.21)	0.276	1.31	(1.03 - 1.66)	0.027
GP practice RTI consultations												
Quintile 1 (lowest RTI consultations)	REF	REF		REF	REF		REF	REF		REF	REF	
Quintile 2	1.16	(1.06 -1.26)	0.001	1.16	(1.03 -1.30)	0.013	1.21	(1.11 - 1.32)	<0.001	1.07	(0.96 - 1.21)	0.234
Quintile 3	1.00	(0.91 -1.11)	0.978	0.99	(0.86 -1.14)	0.907	1.03	(0.93 - 1.14)	0.561	0.96	(0.84 - 1.11)	0.601
Quintile 4	1.07	(0.96 - 1.18)	0.234	1.06	(0.91 - 1.23)	0.487	1.12209	(1.01 - 1.24)	0.029	0.96	(0.82 - 1.11)	0.547
Quintile 5 (highest RTI consultations)	1.33	(1.17 - 1.5)	<0.001	1.19	(1.00 - 1.43)	0.056	1.23	(1.09 - 1.39)	0.001	1.00	(0.84 - 1.2)	0.962
Region												
North East	REF	REF					REF	REF				
North West	0.51	(0.43 - 0.6)	<0.001				0.68	(0.57 - 0.82)	<0.001			
Yorkshire and the Humber	0.67	(0.53 - 0.85)	0.001				0.69	(0.54 - 0.88)	0.003			

Variable	Not prescribed antibiotics - Complication event within 30 days (n=1,561,291)						Prescribed antibiotics - Complication event within 30 days (n=1,404,611)					
	Adjusted OR	95% CI	*P* value	Adjusted OR & Multilevel model	95% CI	*P* value	Adjusted OR	95% CI	*P* value	Adjusted OR & Multilevel model	95% CI	*P* value
East Midlands	1.01	(0.67 - 1.53)	0.955				1.08	(0.63 - 1.85)	0.784			
West Midlands	0.55	(0.47 - 0.65)	<0.001				0.65	(0.55 - 0.78)	<0.001			
East of England	0.59	(0.5 - 0.70)	<0.001				0.75	(0.62 - 0.9)	0.002			
South West	0.67	(0.57 - 0.79)	<0.001				0.82	(0.68 - 0.98)	0.030			
South Central	0.56	(0.48 - 0.66)	<0.001				0.72	(0.61 - 0.87)	<0.001			
London	0.46	(0.39 - 0.54)	<0.001				0.51	(0.43 - 0.62)	<0.001			
South East Coast	0.45	(0.38 - 0.53)	<0.001				0.56	(0.47 - 0.67)	<0.001			

6.4 Discussion

6.4.1 Summary of main findings

This chapter analysed primary care health records of a large representative population which were linked with hospital and mortality data, and provides the first findings of patient-level adjusted analysis of the effects of the QP 2015/16. The adjusted odds ratio, after controlling for clustering at general practice and region levels, shows an increased association of developing RTI complications for patient's post-QP compared to patients' odds pre-QP, with a 7% on average increased odds (p<0.05). This insinuates that the null hypothesis of no difference between pre- and post-QP RTI consultations developing complications can be rejected.

Chapter 5 demonstrated that the occurrence of respiratory complications consulted for in primary care and hospital admissions was on a gradual rise throughout the study period (p<0.05) prior to the introduction of the QP. Hence the significant increase in complications may be indicative of a significantly growing trend in complications, and may be overestimating impacts of the QP by reporting observed effects which may be an extension of what was occurring regardless of the intervention [205, 206, 208] (see section 3.6 which discusses threats to validity using a pre-post analysis design). Increased hospital admissions for pneumonia have been reported over time, despite growing coverage in the elderly of influenza and pneumococcal vaccinations.[177] An increasing trend in sepsis has also been reported.[259]

The results from this chapter corroborate what has been published on increasing probability of complications with age, a recent study suggested that being elderly (and frailty) were associated with greater risk of sepsis and that the probability of sepsis was higher in males compared to females (although the number needed to treat was higher amongst females).[259] This published research also found that the probability of sepsis was lower if antibiotics were prescribed, and is in line with findings from Chapter 2. However, the hierarchical multivariable model outputs which assessed the impact of the QP separately on patients who had not and those who had been prescribed antibiotics, found that

the odds of complication post-QP were higher than the odds of complications pre-QP in patients who had been prescribed antibiotics (OR: 1.07 and 1.09 respectively, $p<0.05$), i.e. whilst both groups of patients (those prescribed and those not prescribed antibiotics) had significantly higher complications post-QP compared to pre-QP, the group who received antibiotics had a stronger measure of association. This is suggestive that patients who had been prescribed antibiotics may have had more severe infections and were higher risk of developing complications, i.e. confounding by indication.[259] Another explanation may be that the increasing incidence of complications may be due to changes in classification and coding over time; for example, more inclusive case definitions and increasing awareness of certain outcomes such as sepsis, as well as the fact that patients with coexisting conditions have also increased over time.[177, 259] Although caution should be placed with the estimates produced due the use of retrospective data, and the use of an exposure that is reliant on two different time points (pre- and post-QP variable identifier), it would be expected that the estimates would identify older age, males and antibiotic use as being associated with greater risk of complications.

6.4.2 Findings in relation to other published evidence

The estimates produced in this chapter are in line with the significant reductions in antibiotic prescribing discussed in Chapter 4 and with published research which substantiates this finding.[33, 92]

The focus of the majority of patient-level studies published, as can be seen in Chapter 2, has been on antibiotic prescribing and their effects on reducing risk of developing RTI complications. This study goes further in that it is not assessing antibiotic prescribing directly, but the implications of a national AMS intervention. A recent published study by Balinskaite and colleagues investigated the impact of the QP national antimicrobial stewardship program on unintended consequences and found that there was no significant association between the QP 2015/16 and a range of clinical complications (selected conditions included: community-acquired and hospital-acquired pneumonia, mastoiditis, quinsy, meningitis, brain abscess, empyema, scarlet fever, and rheumatic fever).[91] This study assessed

aggregated trends and although it standardised rates by age and sex, it did not link patient-level data and assessed outcomes without knowledge of prior healthcare interaction or whether the patient had a previous RTI consultation or antibiotics prescribed.[91] The study was not able to differentiate whether the lack of significant association between the QP and complications was due to ecological fallacy or to changes in the trend of complications measured (i.e. infection rates), as not all patients who may have developed a severe infection evaluated in the study, such as sepsis, would have presented previously in primary care; i.e. these patients and their clinical outcomes would not have been affected by an intervention targeted at primary care.[91] The analyses in Chapter 5, which included patients who had presented with a RTI and linked data, similarly to the study by Balinskaite and colleagues suggested that the introduction of the QP did not have a significant association with complications, although it did suggest that the elderly were at an increased risk of mortality.

6.4.3 Strengths and limitations

The strength of the research in this chapter lies in the large number of patients included and the linkage across healthcare setting (using large national databases) to identify interactions and outcomes across multiple settings and provide a clearer picture to whether outcomes of RTI complications had occurred and been effected by the introduction of the QP 2015/16. The data are reflective of general practice and patient behaviour and is generalisable and representative of the population.

Although the covariates used attempted to account for any confounding effects and residual bias in the effect measure, there were other potential confounders which could have been used to improve the models and have been stated in the literature as potentially influencing the effect on the outcome, such as: smoking status, chronic disease and comorbidities (such as heart disease, lung disease [asthma], diabetes), practice deprivation index (although certain literature suggests deprivation did not have statistically significant effects).[126]

Furthermore, although antibiotic prescribing was assessed, future studies might be designed to compare the type of antibiotic or whether broad-spectrum or narrow-spectrum antibiotics were prescribed. Prescribing of antibiotics could not differentiate antibiotic adherence to the prescription, or whether suboptimal prescriptions were provided (suboptimal dose or length of treatment). Lack of adherence or suboptimal prescribing could reduce the efficacy of antibiotic treatment in terms of curing infections and preventing complications. Obtaining these variables may provide additional insight into antibiotic use and complications, however the data used are representative of the community setting, to everyday clinical practice and to implications of the QP.

6.4.4 Conclusions

Observations suggest a significant (crude) 14% decrease in antibiotic prescribing and a (adjusted) 7% increase in the odds of a complication post-QP compared to the odds pre-QP in complications in England. However, the plausible view that reducing antibiotic prescribing would have a subsequent impact of increased and prolonged carriage and transmission of bacterial respiratory pathogens which would lead to an increase in reported complications has not been substantiated. Rather, the findings are suggestive that patients who had been prescribed antibiotics may have had more severe infections and were at higher risk of adverse health outcomes. The risk of complications and the benefits of antibiotics is highly age-dependent and may be more significant for elderly patients. Antibiotic prescribing reductions may be safer in non-elderly age groups and, to a lesser degree, associated impacts were less probable in females.

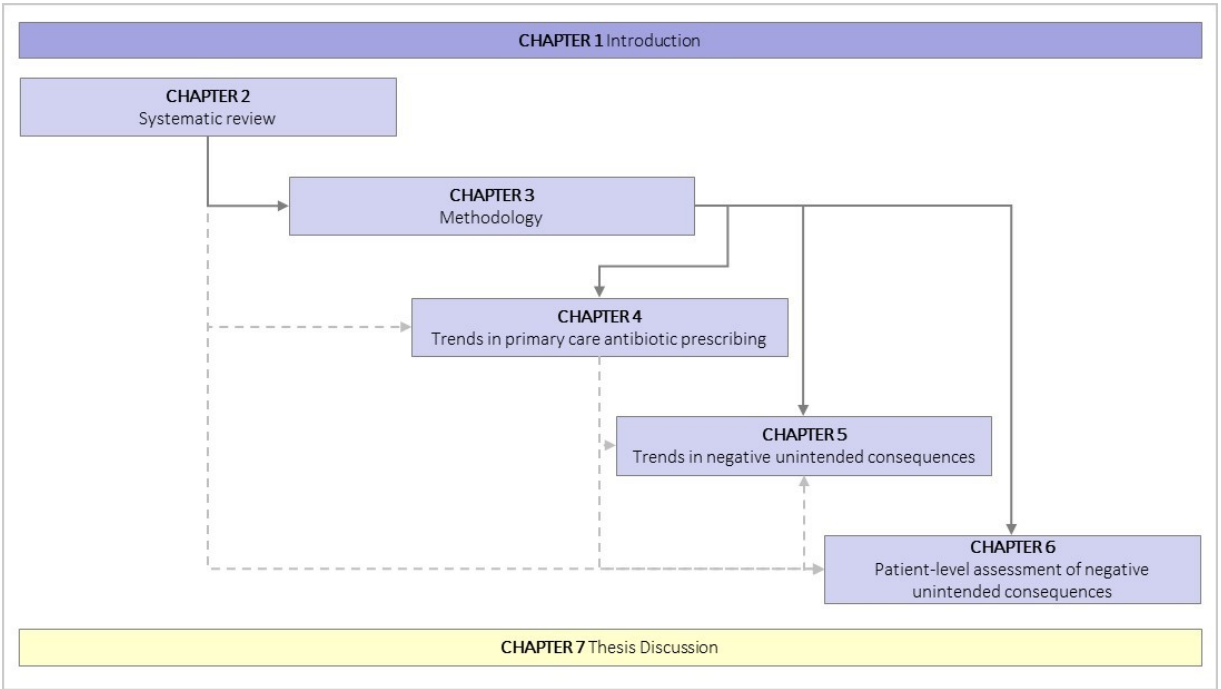
6.4.5 Recommendations and implications for practice or research

Complimenting the recommendations suggested in Chapter 5 which also assessed the unintended consequences of the QP, this study highlighted the patient characteristics most associated with risk of

developing RTI complications, namely the elderly, male gender, and patients who have been prescribed antibiotics. The findings suggest that future primary care antibiotic prescribing interventions should take into account the different risk groups, and that perhaps roll out of interventions should not be extended to all ages, since complications occur in the elderly more than other age groups.

Furthermore, future AMS recommendations and strategies may benefit from targeted implementation and assessment by diagnosis group. Other diagnoses or infection groups such as urinary tract infections and skin and soft tissue infections, which are also commonly prescribed antibiotics in primary care, would benefit from similar research as these patients may have different risks for developing complications. This would be particularly useful as the subsequent QP guidance was updated encouraging specific reductions in antibiotic prescribing for urinary tract infections.[65]

CHAPTER 7


CHAPTER 1 Introduction
CHAPTER 2
Systematic review
CHAPTER 3
Methodology
CHAPTER 4
Trends in primary care antibiotic prescribing
CHAPTER 5
Trends in negative unintended consequences
CHAPTER 6
Patient-level assessment of negative unintended consequences
CHAPTER 7 Thesis Discussion

7 THESIS DISCUSSION

7.1 Principal thesis findings

The motivation behind this thesis was to explore whether a national intervention (the QP 2015-16) had the intended impact of reducing antibiotic prescribing in primary care and examine whether there were any negative unintended consequences following the implementation of this intervention. The focus was on assessing changes in prescribing in relation to RTIs, the most common clinical indication consulted for in primary care, and linking healthcare data across settings to detect potential complications related to prior consultations for uncomplicated RTIs. The benefits of prescribing antibiotics for uncomplicated RTIs is debateable and a highly important question to answer at a time where prudent prescribing is imperative, as a means of reducing the pressure for emergence of antibiotic resistance. However, reducing antibiotic prescribing in primary care should not be at the expense of increasing the risk to patient safety by increasing the likelihood of more severe infections, re-consultations, hospital admissions, or mortality.

Furthermore, where NHS resources are scarce, interventions (particularly those which are financially incentivised), should be evaluated. The analyses undertaken and reported in this thesis contribute to identifying whether the QP was successful in reducing prescribing for RTIs and whether any reduction was associated with adverse clinical consequences.

The thesis first systematically reviewed the published literature to estimate the potential protective effect of antibiotic use in preventing clinical complications of RTIs. Chapter 2 found that early initiation of appropriate antibiotic treatment was associated with a modest improvement in symptom severity and duration, as well as better clinical outcomes (relative to patients not receiving antibiotics) for RTIs by preventing complications and propagation of infection, albeit that these outcomes were rare. The pooled odds ratio of the 28 individual-level studies included was 1.77 (95% CI 1.21-2.57) favouring the

use of antibiotics, i.e. the likelihood of a complications was greater in patients who were not prescribed antibiotics compared to those who were. The effect size of this association became stronger when data for children were assessed separately in a sub-analysis. A key finding throughout was that complications were nonetheless rare, this was also reported in other systematic reviews assessing complications of certain respiratory indications (with the majority of reviews finding no evidence of protective effects of antibiotics for RTIs).[103, 159-162] The studies included in the review suggested homogeneity within the experimental design studies included, however, these often had small sample sizes. Conversely, the observational studies, which were more often largely powered were subject to bias, primarily by indication,[259] and were vastly heterogenous. Hence, future research (as reported in the subsequent chapters) would benefit from having a sample size large enough to detect rare outcomes, aimed primarily at assessing the occurrence of complications, both in the overall population as well as within defined age groups and infections groups.

The review provided an indication as to the clinical complications which should be assessed further and assisted in informing a Delphi method (Chapter 3) utilised to identify respiratory infection pathways. This outlined the index uncomplicated RTIs which are often consulted for in primary care and identified the severe unintended complications which could arise where antibiotics are not prescribed. Chapter 3 provided a comprehensive detailing of the data sources utilised, the linkage and management of data, and defined the statistical methods used in the subsequent chapters, including interrupted time series analysis and hierarchical multivariable logistic regression.

Chapter 4 aimed at identifying whether the QP had its intended impact on antibiotic prescribing in primary care. The propensity to prescribe antibiotics was significantly reduced following the introduction of the QP, both with regards to the numbers of patients consulting (i.e. rate using RTI consultations) and based on the patient population (i.e. registered patients). The incidence of RTIs and antibiotic prescribing were correlated to seasons of the year (winter period), hence the seasonal

adjustments using ITSA improved the validity of these findings, albeit that there is risk of ecological fallacy. Research performed in the UK, Sweden, The Netherlands and the USA suggested declining trends in antibiotic prescribing for RTIs.[3, 77, 172, 242] Nonetheless, published evidence assessing the impact of the QP corroborated the findings from this thesis and reported a much greater relative reduction of 8.2% 24-months after the introduction of the QP for total antibiotic prescribing in primary care (unrelated to indication),[92] and 13% decrease in antibiotic prescriptions (between 2013 and 2017) reported in the 2018 ESPAUR Report.[231]

Having established the QP-associated reductions in prescribing in Chapter 4, Chapter 5 focused on measuring any related unintended consequences of the QP. Unintended consequences were assessed based on whether there were increases in repeat consultations (a proxy for treatment failure), or occurrences of more severe infections (reported in primary and secondary care) termed complications, or death. This chapter found no significant difference in re-consultation rate, or proportion, either overall or by age group, although slight reductions in the level and trend post-QP were visible. Having found little evidence of a negative impact on the use of health services in primary care for similar RTIs, the next sections of Chapter 5 assessed the implications on RTI complications and found that there were no significant correlations with an increase in complications in patients post-QP.

Where significant increases were seen in complications post-QP, these were associated with patients who had been prescribed antibiotics rather than those who had not (hence unrelated to the impact of the QP), and for elderly patients ([≥65 years] thought to be related to predisposing comorbidities), and for complications of pneumonia (thought to be related to a potential "code drift" or a change in disease labelling over the years,[246] as well as an ageing population and associated comorbidities,[177, 259] or limited effectiveness of the PPV23 pneumococcal vaccine amongst the elderly,[202, 246-248]) reported in primary care.

The analysis of hospital admissions for complications permitted assessment of infections which are indicative of greater severity than those consulted in primary care, as they require further treatment,

admission and care. These infections are more costly to health systems and have greater implications to individuals. The findings in secondary care were aligned with those seen in primary care, in that there were no significant consequences on patient outcomes for total complications. Subgroup and sensitivity analysis however revealed a correlated increase in overall complications in patients who were prescribed antibiotics (i.e. these patients would not have been affected by the implementation of QP) and in BSIs (p>0.05, this may have been related to CQUIN scheme simultaneously introduced in March 2015, which set guidance for hospitals to improve early identification and treatment of sepsis.[251] Alternatively, coding sequence changes in 2016 related to primary code and sepsis may account to some extent for increases seen.[189, 252]). Notably the occurrence of complications were rare across both settings, and complications consulted for in primary care and in secondary care were shown to be on a gradual rise prior to the introduction of the QP. Complications in secondary care were more prevalent amongst the elderly population, which was substantiated with the greater mortality seen in this age category within 30-days of an RTI primary care consultation. There was a significant increased level of all-cause mortality within 30-days of an RTI consultation correlated with the introduction of the QP, this was perhaps related to lower than average influenza vaccine effectiveness in 2014/15. [228, 254-257] Statistically significant reductions in the slope of the trend however resulted in patients post-QP exhibiting reduced mortality levels in comparison to what would have been expected had the pre-QP trend continued. Furthermore, patients who had not been prescribed antibiotics did not exhibit greater rates of mortality compared to those who had been prescribed antibiotics at their initial RTI consultation.

Findings from Chapter 5 suggest that the reductions in antibiotic prescribing, the correlated impact of the QP, did not have associated statistically significant unintended consequences. Further assessment of the implications for the elderly, as well as trends in pneumonia in primary care and BSI in secondary care should be monitored. Inferences using the findings from chapter 5 should note that the outcomes were rare and in instances small counts, the data was aggregated from across England hence interpretations are susceptible to ecological fallacy and can't be used to ascertain cause and effect.

Recent published literature substantiates the finding of no significant association between the introduction of the 2015/16 QP on unintended consequences (which included community-acquired and hospital-acquired pneumonia, mastoiditis, quinsy, meningitis, brain abscess, empyema, scarlet fever, and rheumatic fever) in primary and secondary care, unrelated to initial consultations. The study reported significant associations by conditions separately, with similar findings as in the thesis, in that, there were also increases in BSIs observed (not significant within the findings of this thesis), as well as decreases in hospital-acquired pneumonia (although findings of an increase in pneumonia in primary care was also observed within this thesis), and scarlet fever in primary care.[91] A research abstract published in Scotland also found no association between an AMS programme (which had an accompanied reduction in population antibiotic prescribing) and hospital admissions for peritonsillar abscess, mastoiditis and community-acquired pneumonia.[258]

Chapter 6 attempted to strengthen confidence in the findings from previous Chapters, using patient-level data and analysis. Rather than assessing increasing severity of infections by setting and mortality separately, as was undertaken in Chapter 5, this chapter combined complications and mortality into a binary outcome of unintended consequence of the QP. Chapter 6 supported the findings in Chapter 4 by identifying a statistically significant decrease in the likelihood of antibiotic prescribing (crude OR: 0.86, 95% CI: 0.85 – 0.86). However, there was a slight increase in the odds of complications post-QP (adjusted OR: 1.07, 95% CI: 1.03-1.13) compared to pre-QP. The odds of a complication for patients who had been prescribed antibiotics at initial RTI consultation increased slightly post-QP, however, patients who were prescribed antibiotics had a greater odds of a complication compared to those who were not. Hence, a reduction in antibiotic prescribing (the QPs intended direct impact) did not increase a patient's likelihood of a severe outcome to a greater degree than those who were prescribed. Furthermore, the increases in complications (across the four-years included in this study) is likely to be reflective of the pre-existing increasing trend in complications, which was apparent in Chapter 5, and may be an artefact for this reason. The literature indeed corroborates this observed upward trend in complications, particularly in pneumonia and sepsis.[177, 259]

7.2 Strengths and limitations

7.2.1 Data sources and measurements

The strength of the CPRD data as a research source lies in the breadth of coverage, large sample size, long-term follow-up, representativeness and data quality, which permits epidemiological associations to be investigated in more detail and provides estimates with a higher level of statistical precision than would be possible with smaller data sources, which was of particular importance for this thesis as the outcomes and complications assessed were rare. Furthermore, using this data source allowed "real life" research in that the study populations were representative and generalisable to the population at large. CPRD was chosen as the primary care data source not only for the attributes mentioned, but the database offers the greatest linkage of primary care data to other databases.[165]

The linkage of patient records to multiple databases (HES and ONS) provided an effective method of expanding the dataset available for analysis, with the integration offering an enhanced granularity of patient-level information.[165] This combined platform allowed investigation of unintended consequences of the QP, with the ability to assess patient-provider interactions, create episodes of care over a period of time and in so doing, permitted analysis of longitudinal patterns across a patient's healthcare pathway. As patients move between primary and secondary care settings, the impact of AMS processes transgress boundaries within integrated healthcare systems, as does AMR. It is therefore useful for research to link data from these care settings, particularly as the complications assessed in this research are diagnosed and managed in multiple settings. Since the data sources are continuously updated, these sources are ideal for researchers to monitor and assess healthcare trends as well as the effectiveness of new interventions, with minimal cost, as using linked existing databases avoids the associated cost of developing new databases/data collection.[166]

Whilst the use of CPRD, HES and ONS are thought of as a strength of this thesis, there are limitations which should be discussed. The collection of information within these databases has not been designed specifically for research purposes, hence the collection of data has not been tailored for a

particular study, the data may lack detailed information on certain variables which may be required. The routine collection of information may affect the precision of data entered and cause misclassification where coding methodologies are not universal and where there is variability in recorded data amongst primary care; for example primary care physicians may code a consultation on the basis of symptoms (such as earache) rather than the clinical diagnosis (acute otitis media).[246] To overcome this, selection of the infections assessed and the related CPRD Read codes were inclusive (including symptoms and viral infections) and were extensively reviewed by a practicing physician. This increased the sensitivity of the analysis as well as accounting for any shifts in coding, diagnostic drift between RTI categories or preference/guidance of different codes used over the course of the study period. Furthermore, previous research suggests that where certain guidance has been implemented this resulted in coding changes and artefact reductions rather than altered prescribing behaviours (e.g. the introduction of the NICE guidelines for no or delayed antibiotic prescribing of upper RTIs in primary care. The guidelines resulted in reductions in prescribing for specific upper RTI diagnoses, with a transferral and an increase in prescribing to non-specific diagnoses which had less stringent guidance[74]). Coding inclusivity aids in overcoming this misclassification.

Chapter 5 revealed a potential increase in the occurrence of BSIs/sepsis. There has been an increased awareness of sepsis and increased detection and clinical recognition of sepsis over recent years.[189, 252] Therefore, this putative increase may not reflect an increase in incidence, but rather an increase in recording and reporting of these severe infections (i.e. increased ascertainment). National guidelines for sepsis ICD-10 coding were updated in October 2016 (reference page 23, point 3 and 4)[253] stating that sepsis should be the principal diagnosis in the coding sequence i.e. coding for the systemic infection is assigned as the first primary code, rather than what previously may have been coded as a localised less severe infection (e.g. pneumonia may have previously been documented as the primary ICD-10 code where a patient was admitted with pneumonia but also rapidly developed sepsis). This

change in coding in the UK was due to clinicians previously rarely documenting sepsis or septicaemia in the admission documentation, often prioritising the documentation of the source of infection instead.[189] Bloodstream infections, bacteraemia, sepsis and septicaemia have historically been difficult to code, with part of the confusion associated with changing terminology, evolving definitions, changes in microbiological tests, and the duration required to ascertainment a BSI.[188, 189] Coding of BSIs and when the diagnosis is recorded impacts on reimbursement in the NHS, with hospital-onset methicillin-resistant *Staphylococcus aureus* BSIs financially costing a Trust per case if deemed to have been hospital-acquired.

As mentioned in Chapter 3 and 4, general practices voluntarily participate in the submission of their data to CPRD. This may mean there is a lack of random sampling as the general practices included in CPRD may represent the "good prescribing" practices. The results may therefore be an underestimation of both the reductions in antibiotic prescribing and the occurrence of potential complications of RTIs. The sample size used here was however large, and research has recently been published to show that the included practices have variation in prescribing behaviours.[50]

Linking databases increased the detection of infectious complications and permitted the differentiation of the severity of infections detected; i.e. patient outcomes seen in primary care would be reflective of outcomes which are possibly less severe and may present more frequently to primary care than to hospitals (Chapter 5). A disadvantage of database linkage was that it invariably led to smaller sample sizes and patient numbers, with the greater decrease in sample size when numerous databases were linked (as in Chapter 6). This is due to exclusions made during the linkage process of patients who do not qualify for data linkage or for data quality reasons.[165] Efforts were made during the data-linkage process to achieve greater patient numbers by only linking two data sources at a time, as described in Chapter 5.

The HES extract utilised used the latest release of the HES APC data linked to CPRD GOLD (set 15), which covered the study period April 1997-July 2017, this included the study period required (Further details in Chapter 3). The data in this extract were provisional, as the data for financial year 2017/18 had not yet been finalised, hence there may have been a slight alteration with the annual review of the data.

As discussed in Chapter 4, there may have been an increased use of "deferred" or "delayed prescribing" in recent years as a mechanism to reduce antibiotic use. These antibiotic prescription types would have been grouped alongside patients with a normal antibiotic prescription, although these "delayed prescribing" patients may well not have had antibiotics dispensed. It was also not possible to assess changes in the duration or dosage of antibiotic prescriptions (i.e. to identify low or suboptimal doses) or measure adherence, all of which may lead to an increased risk of selecting for resistance and treatment failures. However, national data have demonstrated that reductions in the number of items prescribed has shown equivalent reductions in standardised volume of prescribing.[77] CPRD provides data on issued prescriptions, whereas other data sources such as Prescribing Analyses and Cost (PACT) data provides information on prescriptions that are dispensed, however this source is limited due to the lack of information on the condition for which antibiotics were prescribed.

The decline in antibiotics prescribed in primary care was only assessed for general practice prescribing, which accounts for approximately 86% of total community prescribing.[231] There has been, however, an increasing trend in prescribing of 16.4% observed in other community settings (such as out-of-hours services, urgent care, walk-in centres) since 2013, albeit this accounts for approximately only 5% of prescribing in primary care.[231] This poses the question of whether patients are obtaining antibiotics from other sources when they have not been prescribed in general practice. It is unclear from the findings from this thesis whether there has been a shift in service provision where patients have not been able to obtain antibiotics through consultation with their general practitioner.[262] There is,

however, reduced availability of diagnostic testing, limited background information on the patients, and an increase in clinical uncertainty with these alternative consultations.[262] Furthermore, research suggests an increase in private providers (both within pharmacies and GPs) offering clinical advice via online forms and video consultations, as well as the availability of antibiotics via online retailers, with sales and shipment of antibiotics which do not require prescriptions, permitting patients to bypass any medical assessment and increasing the likelihood of inappropriate use of antibiotics (inappropriate in the availability/use, dose or duration).[262] Research to quantify the extent of prescribing via these alternate routes, and whether a true population reduction was obtained would be beneficial, although the extent of this activity would be difficult to quantify and may not be possible to monitor with limited data available.

7.2.2 Study designs and analyses

In practice, there is no one study design or statistical analysis which provides a comprehensive solution for eliminating all potential sources of bias and confounding. The best analyses often use differing and additional tests in conjunction, to better identify the plausibility of any causal inference. Two different main analyses were therefore used to provide a stronger basis as to whether the results ascertained were robust and reliable: ITSA and hierarchical multivariable modelling. Collectively these statistical methods, along with the sensitivity and several subgroup-analyses, addressed different sources of bias and the somewhat consistent findings increased confidence in the generalisability of the correlations which were demonstrated.

The two statistical methods used complimented each other, in that, the ITSA aggregated data, hence inferences made regarding risk factors and outcomes were prone to ecological fallacy (where inferences may not be applicable at the individual level within the population), whereas the multivariable modelling utilised individual-level data. Nonetheless, analysing the trends in prescribing and complications, at the England population-level is of importance, as this provides a general

impression of prescribing over time and any subsequent complications at the level of which the intervention was implemented.

The use of ITSA to assess the impact of an intervention is relatively novel in the healthcare research field, with this method being previously largely used in econometric studies. This research design is commonly used for evaluation of longitudinal effects of interventions, and is particularly appropriate for population-level interventions that target population-level health outcomes.[209, 211] The rationale for using an ITSA was that analysis across numerous time points can demonstrate patterns of response to the intervention, whilst any changes in population characteristics associated with the outcome are thought to remain relatively constant throughout the study period, or would change slightly and if so would be captured in the linear trend. There are however threats to validity which have been detailed in the literature,[206, 210, 217, 218] outlined in Table 7-1. The effect of the QP intervention using an ITSA was estimated by any change seen following its introduction, compared with the counterfactual expected ongoing trend had the QP not been introduced. The advantage of using a pre-QP population compared to a post-QP population, is that this limits selection bias and confounding related to differences between the groups being compared.[218] The analysis is largely unaffected by typical confounding variables, such as age distribution or socio-economic status, which are thought to remain relatively constant over time in the population. Time-varying confounders which change more rapidly with time, such as seasonality, may however introduce a bias to the interpretation of results, and this was controlled for in the regression models of the ITSA.[211] The fact that the analyses carried out assessing the QP intervention were part of planned research and not as a response to unusually high complications/infections protects the studies against regression to mean effects (Table 7-1), which is common in ITSA research.[218, 263]

History (the likelihood that another event or intervention other than the one assessed has influenced and is the cause of the results observed) is the principle threat to internal validity in the single group ITS design and is also cause for concern within the hierarchical multivariable modelling. It is for this

reason that a mapping of other interventions, guidance, meetings and initiatives were assessed (Figure 1-2, Chapter 1.3.1), to identify whether other interventions were occurring simultaneously and may, in part, be attributable to the effects seen. As mentioned in Chapter 5, the correlated increase in BSIs may be in relation to a competing intervention (Commission for Quality and Innovation [CQUIN] scheme) which was simultaneously introduced in March 2015, and set guidance and incentivised hospitals to improve early identification and treatment of sepsis.[251] Indirect interventions have also been seen to have a subsidiary impact on antibiotic prescribing, with a Canadian policy implemented to provide free universal influenza immunisations associated with a 64% reduction in inappropriate antibiotic prescriptions for influenza related consultations.[264] Similar studies in the United States and Europe also demonstrated reductions in antibiotic prescribing following the use of the pneumococcal conjugate vaccine (PCV),[265, 266] with findings from the UK showing 14.5% fewer amoxicillin prescriptions given during the influenza virus circulation period.[265] This may be due to a reduction in the incidence of febrile illnesses that would often otherwise lead to antibiotic use, such as AOM in children, or additionally due to herd immunity with the indirect protection provided through reduced transmission from those vaccinated to unvaccinated members of the population.[266]

Instrumentation (a change in how the time series and related outcomes are measured over time) is another threat to internal validity, which would have been impacted on by the introduction of CQUIN. Attenuating for other sources of instrumentation or measurement bias in the design and evaluation of effects observed was completed in the analyses via a change in the duration of the study period assessed, calculations of rates, sub-analyses of different outcome codes (the use of R codes for example within HES secondary complication definitions).

Table 7-1. Threats to internal validity with ITSA

Threat to validity	Epidemiological term
History: Other interventions or events occurring pre- or post- intervention, at a similar time point or the same time as the intervention being assessed (the QP), which may cause confusion as to which to attribute to the potential change in outcome assessed. These other events could therefore provide an alternative explanation to the observed effect.	Confounding interventions, or alternate interventions which act as effect modifiers.
Maturation: Naturally occurring changes over the study duration and over time which could be confused with the outcome measurement observed, such as patients in the study growing older, becoming more aware of antimicrobial stewardship, or becoming healthier between the pre- and post-measurement.	Time-varying confounders; variable which change over time.
Instrumentation and testing: A change in the outcome measurement, e.g. change in coding guidance, or a GP changes the way they code certain infections, rather than there being a reduction in those particular infections or related antibiotic prescribing. Being tested or observed can impact on subsequent observations, impacting on treatment effect.	Information bias or measurement bias. Experimenter bias or the observer/ Hawthorne effect, where there is alteration in how a GP or patient alters behaviour due to increased awareness of being observed.
Regression: Values which naturally change over time, or changes due to chance can be confused with the effects observed, e.g. regression to the mean can occur when an intervention is introduced because of recent extremes in some measures, and there is a tendency for the subsequent measures to be less extreme as the initial extreme measure may have been due to random variation and is subsequently mistaken for treatment effect of the intervention.	Statistical regression to the mean or artefact due to random variation or chance.
Selection: Selection bias occurs when there are systematic differences in the characteristics of patients between those receiving the intervention and the comparison group, which could influence the outcome observed, i.e. conclusions drawn are due to differences in populations being compared rather than to the intervention.	Selection bias and variation in confounding factors within the intervention and comparison groups.
Ambiguity of temporal relationship: where there is a lack of clarity about which came first, the cause or the effect/ the exposure or the outcome. In some cases, it may be that the outcome caused the exposure, known as reverse causality. This is less of a concern when the timing of an intervention is known.	Temporal ambiguity and reverse causality.
Attrition: Loss of patient information/participants in the follow-up whilst measuring the outcomes. If there are differences in the people lost to follow-up between pre- and post- observations (the comparison group), then this may be attributable to the differences observed between the two groups.	Loss to follow-up

Parts of the table were sourced from Shadish *et al*. 2002.[206]

7.3 Contributions of the thesis in supporting government policy recommendations

The research findings presented in this thesis are aligned with and can contribute to several government policies and national measures. The most recent have been outlined in Table 7-2.

Table 7-2. Thesis contributions and relevance to national policy and guidance

Intervention/ policy	Objectives	Findings from the thesis	Chapter reference
Quality Premium 2015/16 & Quality Premium 2016/17[64, 65]	Decrease in total and broad-spectrum antibiotic use, with a focus on primary care.	Decrease prescribing of total antibiotic use for patients who consulted with uncomplicated RTIs in England, correlated with the introduction of the QP.	4
Quality Premium 2015/16[64]	Avoidance of emergency admissions for acute conditions that should not usually require hospital admission (adults) and with lower RTIs (children).	No significant complications in hospital admission, except for increase in patients who were prescribed antibiotics (i.e. not effected by the QP) and in BSIs. Complications in secondary care were more prevalent amongst the elderly. Chapter 6 found a slight increase in the odds of complications post-QP compared to pre-QP; likely due to the pre-existing increasing trend. Patients who were prescribed antibiotics had a greater likelihood of a complication compared to those who were not.	5 & 6
Quality Premium 2017-19[66]	Entirely focused on reducing Gram-negative Bloodstream Infections (GNBSIs) and inappropriate antibiotic prescribing in at risk groups (UTIs).	No significant consequences in hospital admission were found, except for an initial increase in the level post-QP of BSIs. Potential increased complications suggested in Chapter 6, may be related to changing trends.	5 & 6
Tackling AMR 2019-2024. The UK's five-year National Action Plan[267]	Optimal use of antimicrobials in humans: - Not only reduce prescribing but ensure timely treatment. - Develop patient-level prescribing and resistance data source (including health and infection outcome and impact data)	No significant difference in re-consultation rate. Significant change in complications reported in primary care for elderly patients (65 years and above) and for complications of pneumonia. As well as the findings stated above in secondary care.	2,3,4,5,6
PHE Patient-level linkage strategy and ESPAUR monitoring of unintended consequences[268]	Undertaking an appraisal of options for monitoring, analysing and disseminating health data for unintended. consequences of changes in antibiotic use in England.[268]	Methods of patient-level data linkage, the respiratory infectious pathways identified, the complications assessed, and the findings discussed above could inform this new surveillance.	2,3,4,5,6

7.4 Overall recommendations and implications

Clinical, policy and public health implications

There was not a significant increase in total complications as an unintended consequence of the QP 2015/16, with further reductions in antibiotic prescribing therefore assumed possible. Recent research has attempted to quantify the level of inappropriate prescribing in English primary care, indicating that even low prescribing general practices are still overprescribing antibiotics and further reductions can be made.[40, 49] Furthermore, the equivalent programme to the QP in Sweden, called STRAMA (which has been in place for more than 25 years), appears to have had a greater impact with reductions of 43% (from 560 to 318 prescription items per 1,000 population) between 1992 and 2016. This suggests that, not only are prescribing rates higher in England compared to Sweden, the Netherlands and the Baltic states, but there is scope to achieve much greater reductions, albeit, there is an argument that there are differences in demographics and patient-mix when comparing internationally. Where further reductions are encouraged, these should be supported by a strong evidence base (e.g. research, surveillance, monitoring) as to the whether these measures are attained and whether there are unintended consequences.

- ***Unintended consequences national surveillance and incorporation into national dashboards:*** Alongside monitoring of incidence of infections, resistance and antibiotic dispensing in primary care, this thesis supports the recommendation to monitor unintended consequences at national level, by implementing national surveillance of unintended consequences. As mentioned above, this is aligned with the National Action Plan, and ESPAUR projects which are already currently being rolled out by Public Health England (PHE) in response to concerns raised by the public and healthcare professionals.[267, 268] The infection pathways, the outcomes assessed, the patient-level linkage of data records, and the methods used throughout this thesis, not only inform on the correlated implications of the QP, but inform and enable a framework for evaluation of AMS initiatives which have been/are being implemented

nationally. The ITS method and infection groups used are being utilised and adopted by PHE, who are building a syndromic surveillance of potential unintended consequences identified in this research. This will permit timely identification of shifts in hospital admission trends which may occur as subsequent on-going reductions in antibiotic prescribing are encouraged and made. Surveillance will provide "information for action" and ensure that a change in trends in complications can be identified and responded to quickly. A mechanism to provide feedback of this data locally would be useful to aid physician decisions relevant to their local populations. This can be accomplished by incorporating the data into existent dashboards, such as the NHS QP Antibiotic Prescribing dashboard (although this is specific to antibiotic prescribing and its longevity is limited) and the PHE Fingertips web portal (AMR local indicators already existent)

(https://fingertips.phe.org.uk/profile/amr-local-indicators).

- ***Linkage, improvement and provision of primary care data:*** In order to obtain surveillance data and monitor trends as suggested above, the integration of primary care data would be pivotal. Data combining patient clinical history (primary care data), social and demographic factors, local bacterial characteristics (e.g. resistance rates and sensitivities to antibiotics, via PHE infection surveillance databases), prescribing, and hospital admissions data would transform primary care data and provide a richness not yet utilised in the UK (or many other countries). Further to the point above, with the inclusion of unintended complications into a dashboard, and alongside the need for primary care data linkage, an important recommendation would be to obtain and provide accessible timely primary care prescribing data by indication (and not only for a sample of the population). This is required to be included in dashboards for future research and surveillance (such as the QP prescribing dashboard, PHE Fingertips, and OpenPrescribing.net), which is primarily of clinical importance to aid in changing prescribing behaviours and adherence to guidance. Additionally, improving the collection of primary care data by providing the addition of a marker to identify antibiotics

which have been prescribed as “delayed” treatment would provide an ability to distinguish these prescriptions to practitioners, researchers as well as policy-makers to better understand the trends in antibiotic prescribing behaviours and decisions. An advantage of a delayed prescribing strategy is that it offers a rapid ‘safety net’ for the small proportion of patients who develop complications or whose symptoms worsen significantly. A patient expecting antibiotics may also be more likely to agree with this course of action rather than with a no prescribing strategy, and this could help to maintain the doctor-patient relationship. This mode of prescription may have increased over the more recent years, however, there is no current method of distinguishing from normal prescriptions.

- ***Development of Clinical Decision Support systems:*** Linkage of large databases in a routine manner, alongside benefits for surveillance purposes, could also be used to form prediction rules or decision-making algorithms to provide rapid guidance based diagnostics, through the use of “Clinical Decision Support Systems” or digital health prescribing tools for primary care practitioners (i.e. computer software which aims to prompt a practitioner at the point of prescribing). This would not only be used as a reminder to primary care practitioners of the importance of AMS but could also be valuable in incorporating local prescribing guidelines and advising on targeting antibiotic prescribing where deemed appropriate and most likely to be beneficial. Awareness of patient groups and indications more at risk of resistance and complications may help rationalise antibiotic use for RTIs, and decision-making tools have in certain instances been suggested as more effective than diagnostic tests in improving antibiotic prescribing (though this is not be the case for complications) and would be cheaper.
- ***Tailored interventions:*** The implications from this research suggests that the presentation, subsequent management of infections and the risk factors for a complicated course are different between patients of different ages, i.e. between children (under 16 years), adults and the elderly (65 years and above). Initiatives targeted at controlling AMR by reducing antibiotic prescribing in adults may not be equally effective in children or the elderly, and/or may have

a different level of impact on unintended consequences whereby vulnerable children and elderly may be at an increased risk of complications, as was demonstrated in both reductions in antibiotic prescribing and in outcomes assessed. The World Society for Paediatric Infectious Diseases (WSPID) has in particularly highlighted that global and national decision makers need to recognise the distinctive nature and significant impact that AMR could have on global neonatal and child health, and further suggests that strategies, research (including research into appropriate antibiotic dosing to maximise clinical outcomes whilst reducing toxicity and selection of AMR) and surveillance need to be specific to neonates and children.[269] Along with specificity of surveillance by age, it would be recommended that future interventions be targeted at particular age groups, or better targeted to certain groups of the population/certain infections (as was subsequently done with the targeted reductions in UTI prescribing encouraged in the subsequent QP[65]). This is particularly relevant as practitioners may deviate from expert-based guidelines when they believe valid risks or reasons behind prescribing, e.g. for the elderly or with children, hence interventions already in place may inadvertently be implicating certain populations/infections more so then others (i.e. targeting populations with no further guidance). Furthermore, research supports this suggestion; that age and indication are important factors to consider. Findings from this thesis suggested that elderly patients with RTIs had an increased level of mortality (although this was not a sustained outcome), and published literature suggests that elderly patients who consult with a UTI in primary care, who were not prescribed an antibiotic or had a deferred prescriptions, were at increased risk of BSIs and mortality compared with patients who were prescribed immediate antibiotics.[163]

- ***Comparison group and cost-effectiveness analyses to inform policy:*** Research around the implementation of the QP by CCGs suggest that national targets (feedback through targets, dashboards, reports) and prioritising the AMS agenda, rather than financial incentives were the levers required in engaging primary care practitioners and implementing improvements in

antibiotic prescribing.[69] With pressure on NHS budgets, scarce resources and numerous initiatives being implemented, there is a need for evidence to identify the opportunity cost of this financially incentivised national AMS intervention and to provide support as to which AMS initiatives are worth investing in. This thesis would recommend a follow-on assessment of:

a) Using a comparison group, such as Scotland, Wales or Northern Ireland, where similar data are available but where the QP was not implemented, or where interventions did not include financial incentives. This would permit the evaluation of whether the financial aspect of the QP were required or whether these populations demonstrated similar reductions in antibiotic prescribing and similar limited variation in complications. In Scotland for example, no such financial incentives were introduced for reductions in BSIs or antibiotic prescribing, however in 2013 a national quality indicator on total antibiotic use in primary care was implemented as part of the Scottish approach to AMS, where practices were required to achieve an equivalent or lower prescribing rate to that of the Scottish 25th percentile.[270]
b) Completing a cost-effectiveness analysis to identify the cost-saving or -spending associated with the QP and whether the NHS spending on this initiative would be, or has been, worthwhile.

Research and epidemiological implications

- ***Antimicrobial resistance:*** Prudent antibiotic prescribing is fundamentally required to reduce antimicrobial resistance and is the motive behind the implementation of the antibiotic prescribing element of the QP 2015/16. Research into the anticipated reduction in antimicrobial resistance by linking prescribing, indication and national routine surveillance data on antimicrobial sensitivities would be beneficial. Such studies have begun with findings

of primary care antibiotic dispensing and reductions in antimicrobial resistance in community-acquired *Escherichia coli* infections.[271]

- ***Assessing other indications (UTIs):*** Widening the methods and assessing other primary care conditions and whether the QP had an impact on other indications would be beneficial, particularly for UTIs, as primary uncomplicated cystitis, for example, may lead to more concerning secondary or severe infections and may have greater tendency compared to RTIs of doing so.[163] This is particularly important as the succeeding QP and on-going interventions specified reductions in antibiotic prescribing specifically for UTI indications,[65] with approximately 40% of antimicrobial prescriptions thought to be inappropriate for treatment of UTIs.[272]
- ***Shifts in prescribing:*** This thesis did not assess prescribing in other settings, such as urgent care centres/walk in centres, out of hours services or other community services. There may have been a shift from prescribing in general practices to other primary care settings. It would be useful to track antibiotic use over time to determine the influence of AMS initiatives in different prescriber populations. Moreover, it would be interesting to identify the interactions and shifts between these settings, in that patients may attend other settings where antibiotics are being "withheld" at the general practice. Physicians at urgent care centres may not have the necessary relationships with patients to discuss antibiotic use and stewardship, particularly if antibiotics are specifically requested by the patient.
- ***COVID-19 related changes in antibiotic prescribing behaviour:*** The impact of the Coronavirus Disease 2019 (COVID-19) pandemic on antibiotic prescribing and subsequent unintended consequences is also of interest. A systematic review on hospitalised COVID-19 patients identified that 72% of patients had received antibiotics, with only 8% demonstrating superimposed bacterial co-infections.[273] Hence, the pandemic has seen wide use of antibiotics, particularly broad-spectrum antibacterials, despite the paucity of bacterial co-infections in secondary care.[273] In primary care, however, there has been a change in both the

presentation of patients and in consultation type, with a move to telehealth. Trends in antibiotic prescribing in the community in Scotland demonstrated an initial surge (March 2020), followed by pronounced reductions (from April 2020) in prescriptions for respiratory antibiotics.[274] This decrease in primary care antibiotic prescribing, the likely decrease in uncomplicated RTIs and other infections which previously would have resulted in consultations in primary care, the impact on antimicrobial resistance and unintended consequences such as potential increased severity of infections where delays in antibiotic treatment may be more likely, are scope for future research.

- ***High- and low-prescribing practices:*** Assessment of antibiotic prescribing using CPRD did not permit assessment by CCGs, as the pseudo-anonymised nature of the data did not have this healthcare hierarchy mapping available. The research (as well as findings in Chapter 6) suggests that there is evident variation in antibiotic resistance and prescribing geographically within England.[15, 231] Evaluation of how the QP has impacted on high- and low- prescribers would be beneficial and scope for further investigation, i.e. whether there was variability in the propensity to prescribe between practices who prior to the QP were higher prescribers.

7.5 Final conclusions

Changing antibiotic prescribing practice so that reductions, specifically targeted reductions of antibiotic prescribing for common infections in primary care, has become a public health necessity. This behavioural change via the implementation of national guidelines constitutes a fine balancing act between individual and societal concerns, the individual concern of potentially increasing the risk of unintended consequences and the societal concern of antimicrobial resistance. The evidence from this thesis shows that national guidance has been safely implemented. There was a corresponding decrease in antibiotic prescribing for uncomplicated respiratory infections associated with the introduction of the QP, and no significant increases in unintended consequences (except in certain instances: for elderly patients [65 years and over] thought to be related to predisposing comorbidities, pneumonia reported in primary care thought in part due to "code drifting", and [insignificant] increase in BSIs in secondary care, which may be explained by an upsurge in screening for sepsis). Further reductions, guidelines and policies would benefit from moving from a "one size fits all" reduction in prescribing however and prescribing behaviour should become more congruent with the growing evidence base, in that prescribing benchmarks should be more focused on the infection indication and patient risk factors. This has already been put into practice with the subsequent amendment of the QP in 2016/17. Further research into the expected gains of reducing national antibiotic prescribing by further linking national routine surveillance data on antimicrobial sensitivities would be the next step in associating whether the presumed impact on antimicrobial resistance is being impacted on. Linking primary care data, and continuous monitoring via dashboards and implementing national unintended surveillance is essential. Where patients, and antimicrobial resistance, move between different healthcare settings, the research and policy agendas should increasingly link these sectors of care.

SCIENTIFIC CONTRIBUTIONS

Title	Type
Balinskaite V, ***Bou-Antoun S***, Johnson AP, Holmes A, Aylin P. An assessment of potential unintended consequences following a national antimicrobial stewardship programme in England: an interrupted time series analysis., Clin Infect Dis. (2019). https://doi.org/10.1093/cid/ciy904 (Appendix 39)	Peer-reviewed publication
"Measuring the potential unintended consequences of national policy aimed at reducing antibiotic prescribing in primary care". The Centre for Medication Safety and Service Quality (CMSSQ) and HPRU in HCAI & AMR joint quarterly meeting. Faculty of Medicine, ICL. Dec 2018	Oral presentation
Bou-Antoun S, Costelloe C, Honeyford K, Mazidi M, Hayhoe BWJ, Holmes A, Johnson AP, Aylin P. Age-related decline in antibiotic prescribing for uncomplicated respiratory tract infections in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis., *J Antimicrob Chemother*, Vol:73, Pages:2883-2892. (2018). https://doi.org/10.1093/jac/dky237 (Appendix 39)	Peer-reviewed publication
"Investigating the trend in primary care antibiotic prescribing for uncomplicated respiratory tract infections". Bou-Antoun S, Johnson AP, Costelloe C, Aylin P. The Medical Research Foundation National PhD Training Programme in AMR conference. Bristol. (Aug 2018).	Conference poster
"Age-related decline in primary care antibiotic prescribing for patients with uncomplicated RTIs following the introduction of the Quality Premium in England: Interrupted time series analysis". ***Bou-Antoun S***, Johnson AP, Costelloe C, Aylin P. 47th Annual Scientific Meeting of the Society for Academic Primary Care (SAPC). Barbican, London. (Jul 2018).	Oral conference presentation
"Investigating the trend in primary care antibiotic prescribing for uncomplicated RTIs". The Child Health Unit research meeting. School of Public Health, ICL. (Nov 2017).	Oral presentation
"Investigating the trend in primary care antibiotic prescribing for respiratory tract infections". ***Bou-Antoun S***, Johnson AP, Costelloe C, Aylin P. The General Practice Research on Infections Network (GRIN) conference. Oslo, Norway. (Sep 2017).	Oral conference presentation
"Measuring the potential unintended consequences of national policy aimed at reducing antibiotic prescribing in primary care". Joint meeting of HPRUs at ICL: HCAI & AMR, Health Impact of environmental Hazards, Modelling Methodology, Respiratory Infections. (Mar 2017)	Oral presentation
"Measuring the potential unintended consequences of national intervention to reduce antibiotic prescribing in primary care". PHE HCAI & AMR Scientific Forum. Colindale. Feb 2017	Oral presentation
Bou-Antoun S, Davies J, Guy R, Johnson AP, Sheridan EA, Hope RJ. Descriptive epidemiology of Escherichia coli bacteraemia in England, April 2012 to March 2014. *Euro Surveill* 21(35). (2016). https://doi.org/10.2807/1560-7917.ES.2016.21.35.30329	Peer-reviewed publication
"Measuring the potential unintended consequences of national intervention to reduce antibiotic prescribing in primary care". The Division of Infectious Diseases and HIV Medicine, Groote Schuur Hospital, research initiative meeting. ICL and Uni of Cape Town: Global Fellows Programme 2016. Cape Town, South Africa. (Jun 2016).	Oral presentation
"Linkage of Big Data to measure the potential unintended consequences of national policy". The Big Data and analytical Unit (BDAU) Data Summit and Researchers Meeting. Institute of Global Health Innovation, ICL. (Oct 2015).	Oral presentation

REFERENCES

1. Fleming A. The discovery of penicillin. *British Medical Bulletin* 1944; **2**: 4-5.
2. Chain E, Florey HW, Gardner AD et al. Penicillin as a chemotherapeutic agent. *The lancet* 1940; **236**: 226-8.
3. Cosby JL, Francis N, Butler CC. The role of evidence in the decline of antibiotic use for common respiratory infections in primary care. *Lancet Infect Dis* 2007; **7**: 749-56.
4. Laxminarayan R, Matsoso P, Pant S et al. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016; **387**: 168-75.
5. O'Neill J. on behalf of The Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf.
6. Costelloe C, Metcalfe C, Lovering A et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *Bmj-Brit Med J* 2010; **340**.
7. Davies JD, D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 2010; **74**: 417-33.
8. World Health Organization W. Antimicrobial resistance. http://www.searo.who.int/thailand/factsheets/fs0023/en/ (03/10/2019 2019, date last accessed).
9. Lewis K. Platforms for antibiotic discovery. *Nat Rev Drug Discov* 2013; **12**: 371-87.
10. Fleming A. Penicillin. https://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf2018, date last accessed).
11. Podolsky SH. The evolving response to antibiotic resistance (1945-2018). *Palgr Commun* 2018; **4**.
12. Holmes AH, Moore LSP, Sundsfjord A et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016; **387**: 176-87.
13. Keith T, Saxena S, Murray J et al. Risk-benefit analysis of restricting antimicrobial prescribing in children: what do we really know? *Curr Opin Infect Dis* 2010; **23**: 242-8.
14. Livermore DM. Globalisation of antibiotic resistance. *Microbiol Aust* 2016; **37**: 198-201.
15. Bou-Antoun S, Davies J, Guy R et al. Descriptive epidemiology of Escherichia coli bacteraemia in England, April 2012 to March 2014. *Eurosurveillance* 2016; **21**: 9-17.
16. Livermore DM. Bacterial resistance: origins, epidemiology, and impact. *Clin Infect Dis* 2003; **36**: S11-23.
17. Naylor NR, Pouwels KB, Hope R et al. The health and cost burden of antibiotic resistant and susceptible Escherichia coli bacteraemia in the English hospital setting: A national retrospective cohort study. *PLoS One* 2019; **14**: e0221944.
18. The Pew Charitable Trusts. A Scientific Roadmap for Antibiotic Discovery. A sustained and robust pipeline of new antibacterial drugs and therapies is critical to preserve public health. http://www.pewtrusts.org/~/media/assets/2016/05/ascientificroadmapforantibioticdiscovery.pdf.
19. Lammie SL, Hughes JM. Antimicrobial Resistance, Food Safety, and One Health: The Need for Convergence. *Annu Rev Food Sci Technol* 2016; **7**: 287-312.
20. White A, Hughes JM. Critical Importance of a One Health Approach to Antimicrobial Resistance. *Ecohealth* 2019; **16**: 404-9.
21. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.
22. Clatworthy AE, Pierson E, Hung DT. Targeting virulence: a new paradigm for antimicrobial therapy. *Nat Chem Biol* 2007; **3**: 541-8.
23. Ling LL, Schneider T, Peoples AJ et al. A new antibiotic kills pathogens without detectable resistance. *Nature* 2015; **517**: 455-+.

24. Castro-Sanchez E, Moore LSP, Husson F et al. What are the factors driving antimicrobial resistance? Perspectives from a public event in London, England. *Bmc Infect Dis* 2016; **16**.
25. Johnson AP, Ashiru-Oredope D, Beech E. Antibiotic Stewardship Initiatives as Part of the UK 5-Year Antimicrobial Resistance Strategy. *Antibiotics-Basel* 2015; **4**: 467-79.
26. Goossens H, Ferech M, Vander Stichele R et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**: 579-87.
27. Bell BG, Schellevis F, Stobberingh E et al. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *Bmc Infect Dis* 2014; **14**.
28. Public Health England P. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). Report 2018 - 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/843129/English_Surveillance_Programme_for_Antimicrobial_Utilisation_and_Resistance_2019.pdf.
29. Klein EY, Van Boeckel TP, Martinez EM et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *P Natl Acad Sci USA* 2018; **115**: E3463-E70.
30. Torumkuney D, Mokaddas E, Jiman-Fatani A et al. Results from the Survey of Antibiotic Resistance (SOAR) 2015-17 in the Middle East (Kuwait, Lebanon and Saudi Arabia): data based on CLSI, EUCAST (dose-specific) and pharmacokinetic/pharmacodynamic (PK/PD) breakpoints. *J Antimicrob Chemother* 2020; **75**: i60-i75.
31. Johnson AP, Enne VI, Perry JD. Preface. *J Antimicrob Chemoth* 2020; **75**: I-I.
32. European Centre for Disease Prevention and Control (An agency of the European Union). Summary of the latest data on antibiotic consumption in the European Union: 2017 https://ecdc.europa.eu/sites/portal/files/documents/Final_2017_EAAD_ESAC-Net_Summary-edited%20-%20FINALwith%20erratum.pdf.
33. Bou-Antoun S, Costelloe C, Honeyford K et al. Age-related decline in antibiotic prescribing for uncomplicated respiratory tract infections in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis. *The Journal of antimicrobial chemotherapy* 2018; **73**: 2883-92.
34. Whitehead M, Dahlgren G. What can be done about inequalities in health? *Lancet* 1991; **338**: 1059-63.
35. Wise R. The relentless rise of resistance? *J Antimicrob Chemoth* 2004; **54**: 306-10.
36. Martinez-Gonzalez NA, Coenen S, Plate A et al. The impact of interventions to improve the quality of prescribing and use of antibiotics in primary care patients with respiratory tract infections: a systematic review protocol. *BMJ open* 2017; **7**: e016253.
37. Public Health England P. English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/362374/ESPAUR_Report_2014__3_.pdf

https://webarchive.nationalarchives.gov.uk/20191003132022/https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report.
38. Borek AJ, Wanat M, Sallis A et al. How Can National Antimicrobial Stewardship Interventions in Primary Care Be Improved? A Stakeholder Consultation. *Antibiotics-Basel* 2019; **8**.
39. Shallcross LJ, Davies DSC. Antibiotic overuse: a key driver of antimicrobial resistance. *Brit J Gen Pract* 2014; **64**: 604-5.
40. Smieszek T, Pouwels KB, Dolk FCK et al. Potential for reducing inappropriate antibiotic prescribing in English primary care. *J Antimicrob Chemother* 2018; **73**: ii36-ii43.
41. Easton G, Saxena S. Antibiotic prescribing for upper respiratory tract infections in children: how can we improve? *London J Prim Care (Abingdon)* 2010; **3**: 37-41.
42. Little P, Rumsby K, Kelly J et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. *Jama* 2005; **293**: 3029-35.

43. Davey P, Rutherford D, Graham B et al. Repeat consultations after antibiotic prescribing for respiratory infection: a study in one general practice. *Br J Gen Pract* 1994; **44**: 509-13.
44. Johnson AP. Surveillance of antibiotic resistance. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 2015; **370**.
45. Hayhoe B, Butler CC, Majeed A et al. Telling the truth about antibiotics: benefits, harms and moral duty in prescribing for children in primary care. *J Antimicrob Chemoth* 2018; **73**: 2298-304.
46. Petersen I, Hayward AC, Subgrp SS. Antibacterial prescribing in primary care. *J Antimicrob Chemoth* 2007; **60**: I43-I7.
47. Dolk FCK, Pouwels KB, Smith DRM et al. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? *The Journal of antimicrobial chemotherapy* 2018; **73**: ii2-ii10.
48. Hutchinson JM, Jelinski S, Hefferton D et al. Role of diagnostic labeling in antibiotic prescription. *Can Fam Physician* 2001; **47**: 1217-24.
49. Pouwels KB, Dolk FCK, Smith DRM et al. Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. *J Antimicrob Chemoth* 2018; **73**: 19-26.
50. Pouwels KB, Dolk FCK, Smith DRM et al. Explaining variation in antibiotic prescribing between general practices in the UK. *J Antimicrob Chemoth* 2018; **73**: 27-35.
51. Gulliford MC, Moore MV, Little P et al. Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care: cohort study using electronic health records. *Bmj-Brit Med J* 2016; **354**.
52. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2013: CD000023.
53. National Institue for Health and Care Excellence N. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. https://www.nice.org.uk/guidance/ng15/chapter/1-Recommendations (21/10/2019.
54. Hopkins S. UK initiatives to reduce antimicrobial resistant infections, 2013-2018. *Int J Health Gov* 2016; **21**: 131-8.
55. Ashiru-Oredope D, Sharland M, Charani E et al. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: Start Smart-Then Focus. *J Antimicrob Chemoth* 2012; **67**: I51-I63.
56. World Health Organization W. Fifty-first World Health Assembly. Emerging and other communicable diseases: Antimicrobial resistance. *WHO* 1998; **Agenda item 21.3**.
57. Standing Medical Advisory Committee. Standing Medical Advisory Committee (SMAC) report: the path of least resistance. http://antibiotic-action.com/wp-content/uploads/2011/07/Standing-Medical-Advisory-Committee-The-path-of-least-resistance-1998.pdf.
58. Davies S. Annual report of the chief medical officer. 2011. Vol 2. Infections and the rise of antimicrobial resistance. . *Department of Health CMO Annual Report* 2013.
59. Davies SG, N. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. *Department of Health, London* 2013.
60. Public Health England P. Start smart then focus: antimicrobial stewardship toolkit for English hospitals. *PHE* 2015.
61. Royal College of Gerenal Practitioners R. TARGET Antibiotics Toolkit. *RCGP* 2015.
62. Davies S, Gibbens N. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. *Department of Health, London* 2013.
63. NHS_England. Quality Premium: 2015/16 guidance for CCGs2015. http://www.england.nhs.uk/wp-content/uploads/2015/04/qual-prem-guid-1516.pdf (Access Date Access 2015, date last accessed).
64. NHS England. Quality Premium: 2015/16 guidance for CCGs. https://www.england.nhs.uk/ccg-out-tool/qual-prem/.
65. NHS England. Quality Premium guidance 2016/17 for CCGs. https://www.england.nhs.uk/ccg-out-tool/qual-prem/.

66. NHS England. Quality Premium guidance 2017-19 for CCGs. https://www.england.nhs.uk/ccg-out-tool/qual-prem/.
67. Johnson AP, Muller-Pebody B, Budd E et al. Improving feedback of surveillance data on antimicrobial consumption, resistance and stewardship in England: putting the data at your Fingertips. *J Antimicrob Chemoth* 2017; **72**: 953-6.
68. Meeker D, Linder JA, Fox CR et al. Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices: A Randomized Clinical Trial. *JAMA* 2016; **315**: 562-70.
69. Anyanwu PE, Borek AJ, Tonkin-Crine S et al. Conceptualising the Integration of Strategies by Clinical Commissioning Groups in England towards the Antibiotic Prescribing Targets for the Quality Premium Financial Incentive Scheme: A Short Report. *Antibiotics (Basel, Switzerland)* 2020; **9**.
70. Anyanwu PE, Tonkin-Crine S, Borek A et al. Investigating the mechanism of impact of the Quality Premium initiative on antibiotic prescribing in primary care practices in England: a study protocol. *Bmj Open* 2019; **9**.
71. Public Health England P. English surveillance programme antimicrobial utilisation and resistance (ESPAUR): report 2017. https://webarchive.nationalarchives.gov.uk/20191003132022/https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report.
72. Van Katwyk SR, Grimshaw JM, Mendelson M et al. Government policy interventions to reduce human antimicrobial use: protocol for a systematic review and meta-analysis. *Syst Rev* 2017; **6**.
73. Talpaert MJ, Gopal Rao G, Cooper BS et al. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of Clostridium difficile infection. *J Antimicrob Chemother* 2011; **66**: 2168-74.
74. Thompson PLS, N.; Sharland, M.; Gilbert, R. E.; Saxena, S.; Long, P. F.; Johnson, A. P.; Wong, I. C. Changes in clinical indications for community antibiotic prescribing for children in the UK from 1996 to 2006: will the new NICE prescribing guidance on upper respiratory tract infections just be ignored? *Arch Dis Child* 2009; **94**: 337-40.
75. Ashiru-Oredope D, Hopkins S. Antimicrobial resistance: moving from professional engagement to public action. *J Antimicrob Chemoth* 2015; **70**: 2927-30.
76. McNulty CAM, Nichols T, Boyle PJ et al. The English antibiotic awareness campaigns: did they change the public's knowledge of and attitudes to antibiotic use? *J Antimicrob Chemoth* 2010; **65**: 1526-33.
77. Gulliford M, Latinovic R, Charlton J et al. Selective decrease in consultations and antibiotic prescribing for acute respiratory tract infections in UK primary care up to 2006. *J Public Health (Oxf)* 2009; **31**: 512-20.
78. Kochling A, Loffler C, Reinsch S et al. Reduction of antibiotic prescriptions for acute respiratory tract infections in primary care: a systematic review. *Implement Sci* 2018; **13**.
79. Ellegard LM, Dietrichson J, Anell A. Can pay-for-performance to primary care providers stimulate appropriate use of antibiotics? *Health Econ* 2018; **27**: e39-e54.
80. Ranji SR, Steinman MA, Shojania KG et al. Interventions to reduce unnecessary antibiotic prescribing - A systematic review and quantitative analysis. *Med Care* 2008; **46**: 847-62.
81. Mayor S. Feedback to GPs reduces antibiotic prescribing, study finds. *Bmj-Brit Med J* 2016; **352**.
82. Van Katwyk SR, Grimshaw JM, Nkangu M et al. Government policy interventions to reduce human antimicrobial use: A systematic review and evidence map. *Plos Med* 2019; **16**.
83. NPCRDC. National Primary Care Research and Development Centre. What difference has QOF made?2009. http://www.population-health.manchester.ac.uk/primarycare/npcrdc-archive/Publications/QOFSpotlight2009.pdf (Access Date Access 2009, date last accessed).
84. Yip W, Powell-Jackson T, Chen W et al. Capitation Combined With Pay-For-Performance Improves Antibiotic Prescribing Practices In Rural China. *Health Affair* 2014; **33**: 502-10.
85. Tonkin-Crine S, Yardley L, Little P. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. *J Antimicrob Chemoth* 2011; **66**: 2215-23.

86. Tonkin-Crine S, Yardley L, Coenen S et al. GPs' views in five European countries of interventions to promote prudent antibiotic use. *Brit J Gen Pract* 2011; **61**.
87. Butler CC, Dunstan F, Heginbothom M et al. Containing antibiotic resistance: decreased antibiotic-resistant coliform urinary tract infections with reduction in antibiotic prescribing by general practices. *Brit J Gen Pract* 2007; **57**: 785-92.
88. Bergman M, Huikko S, Pihlajamaki M et al. Effect of macrolide consumption on erythromycin resistance in Streptococcus pyogenes in Finland in 1997-2001. *Clinical Infectious Diseases* 2004; **38**: 1251-6.
89. Cars T, Eriksson I, Granath A et al. Antibiotic use and bacterial complications following upper respiratory tract infections: a population-based study. *Bmj Open* 2017; **7**.
90. Little P, Stuart B, Smith S et al. Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study. *Bmj-Brit Med J* 2017; **357**.
91. Balinskaite V, Bou-Antoun S, Johnson AP et al. An Assessment of Potential Unintended Consequences Following a National Antimicrobial Stewardship Program in England: An Interrupted Time Series Analysis. *Clin Infect Dis* 2019; **69**: 233-42.
92. Balinskaite V, Johnson AP, Holmes A et al. The Impact of a National Antimicrobial Stewardship Program on Antibiotic Prescribing in Primary Care: An Interrupted Time Series Analysis. *Clin Infect Dis* 2019; **69**: 227-32.
93. Livermore DM. Minimising antibiotic resistance. *Lancet Infectious Diseases* 2005; **5**: 450-9.
94. Autret-Leca E, Giraudeau B, Ployet MJ et al. Amoxicillin/clavulanic acid is ineffective at preventing otitis media in children with presumed viral upper respiratory infection: a randomized, double-blind equivalence, placebo-controlled trial. *Brit J Clin Pharmaco* 2002; **54**: 652-6.
95. Dagnelie CF, VanderGraaf Y, DeMelker RA et al. Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. *Brit J Gen Pract* 1996; **46**: 589-93.
96. Little P, Gould C, Williamson I et al. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ (Clinical research ed)* 1997; **315**: 350-2.
97. Hay AD, Thomas M, Montgomery A et al. The relationship between primary care antibiotic prescribing and bacterial resistance in adults in the community: a controlled observational study using individual patient data. *J Antimicrob Chemoth* 2005; **56**: 146-53.
98. Hillier S, Roberts Z, Dunstan F et al. Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case-control study. *J Antimicrob Chemoth* 2007; **60**: 92-9.
99. McCormick DP, Chonmaitree T, Pittman C et al. Nonsevere acute otitis media: A clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics* 2005; **115**: 1455-65.
100. Bucher HC, Tschudi P, Young J et al. Effect of amoxicillin-clavulanate in clinically diagnosed acute rhinosinusitis: A placebo-controlled, double-blind,randomized trial in general practice. *Arch Intern Med* 2003; **163**: 1793-8.
101. Galvao MGA, Santos MARC, da Cunha AJLA. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. *Cochrane Db Syst Rev* 2016.
102. Hu YH, Walley J, Chou R et al. Interventions to reduce childhood antibiotic prescribing for upper respiratory infections: systematic review and meta-analysis. *J Epidemiol Community Health* 2016; **70**: 1162-70.
103. Falagas ME, Giannopoulou KP, Vardakas KZ et al. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. *Lancet Infectious Diseases* 2008; **8**: 543-52.
104. Smith SM, Fahey T, Smucny J et al. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2017; **6**: CD000245.

105. Spurling GK, Del Mar CB, Dooley L et al. Delayed antibiotics for respiratory infections. *Cochrane Database Syst Rev* 2013: CD004417.
106. Venekamp RP, Sanders SL, Glasziou PP et al. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2015: CD000219.
107. Lemiengre MB, van Driel ML, Merenstein D et al. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. *Cochrane Database Syst Rev* 2012; **10**: CD006089.
108. Moher D, Shamseer L, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Rev Esp Nutr Hum Die* 2016; **20**: 148-60.
109. Thomas J, Graziosi S, Brunton J et al. EPPI-Reviewer: advanced software for systematic reviews, maps and evidence synthesis. . https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2935.
110. Methley AM, Campbell S, Chew-Graham C et al. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *Bmc Health Serv Res* 2014; **14**.
111. Zwart S, Sachs APE, Ruijs GJHM et al. Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. *Brit Med J* 2000; **320**: 150-4.
112. Zwart S, Sachs APE, Ruijs GJHM et al. Penicillin B for acute throat infections in adults: Rapid resolution of symptoms after a 7-day treatment as compared to a 3-day treatment or a placebo; a randomized double-blind study. *Nederlands Tijdschrift voor Geneeskunde* 2001; **145**: 629-34.
113. Critical Appraisal Skills Programme. Critical Appraisal Skills Programme (2017). CASP (Cohort Study) Checklist. http://media.wix.com/ugd/dded87_5ad0ece77a3f4fc9bcd3665a7d1fa91f.pdf (04/04/2017 2017, date last accessed).
114. Critical Appraisal Skills Programme. Critical Appraisal Skills Programme (2017). CASP (Case-Control Study) Checklist. http://media.wix.com/ugd/dded87_afbfc99848f64537a53826e1f5b30b5c.pdf (04/04/2017 2017, date last accessed).
115. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. https://training.cochrane.org/handbook/current (11/05/2020.
116. Centre for Reviews and Dissemination C. Systematic Reviews. CRD's guidance for undertaking reviews in health care. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (12/05/2020.
117. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. *Systematic reviews in health care: meta-analysis in context* 2001: 285-312.
118. Dickersin K. The Existence of Publication Bias and Risk-Factors for Its Occurrence. *Jama-J Am Med Assoc* 1990; **263**: 1385-9.
119. Sterne JAC, Sutton AJ, Ioannidis JPA et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *Bmj-Brit Med J* 2011; **343**.
120. Chapple PAL, Franklin LM, Paulett JD et al. Treatment Of Acute Sore Throat In General Practice: Therapeutic Trial, With Observations On Symptoms And Bacteriology. *The British Medical Journal* 1956; **1**: 705-8.
121. Demeyere M, Mervielde Y, Verschraegen G et al. Effect of Penicillin on the Clinical Course of Streptococcal Pharyngitis in General-Practice. *European Journal of Clinical Pharmacology* 1992; **43**: 581-5.
122. De Sutter AI, De Meyere MJ, Christiaens TC et al. Does Amoxicillin improve outcomes in patients with purulent rhinorrhea? A pragmatic randomized double-blind controlled trial in family practice. *J Fam Practice* 2002; **51**: 317-23.
123. Howe RW, Millar MR, Coast J et al. A randomized controlled trial of antibiotics on symptom resolution in patients presenting to their general practitioner with a sore throat. *Brit J Gen Pract* 1997; **47**: 280-4.
124. Howie JG, Foggo BA. Antibiotics, sore throats and rheumatic fever. *J R Coll Gen Pract* 1985; **35**: 223-4.

125. Crocker JC, Powell CVE, Evans MR et al. Paediatric pneumonia or empyema and prior antibiotic use in primary care: a case-control study. *J Antimicrob Chemoth* 2012; **67**: 478-87.
126. Dunn N, Lane D, Everitt H et al. Use of antibiotics for sore throat and incidence of quinsy. *Brit J Gen Pract* 2007; **57**: 45-9.
127. Fry J. Antibiotics in acute tonsillitis and acute otitis media. *Brit Med J* 1958; **2**: 883.
128. Little P, Moore M, Kelly J et al. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. *Bmj-Brit Med J* 2014; **348**.
129. Little P, Stuart B, Hobbs FD et al. Antibiotic prescription strategies for acute sore throat: a prospective observational cohort study. *Lancet Infect Dis* 2014; **14**: 213-9.
130. Marchetti F, Ronfani L, Nibali SC et al. Delayed Prescription May Reduce the Use of Antibiotics for Acute Otitis Media: A Prospective Observational Study in Primary Care. *Archives of Pediatrics & Adolescent Medicine* 2005; **159**: 679-84.
131. Meropol SB, Localio AR, Metlay JP. Risks and benefits associated with antibiotic use for acute respiratory infections: a cohort study. *Ann Fam Med* 2013; **11**: 165-72.
132. Mygind N, Meistruplarsen KI, Thomsen J et al. Penicillin in Acute Otitis-Media - a Double-Blind Placebo-Controlled Trial. *Clin Otolaryngol* 1981; **6**: 5-13.
133. Petersen I, Johnson AM, Islam A et al. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *Brit Med J* 2007; **335**: 982-4a.
134. Stalman W, VanEssen GA, VanDerGraaf Y et al. The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? A placebo-controlled double-blind randomized doxycycline trial. *Brit J Gen Pract* 1997; **47**: 794-9.
135. Tahtinen PA, Laine MK, Huovinen P et al. A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media. *New Engl J Med* 2011; **364**: 116-26.
136. Taylor JL, Howie JG. Antibiotics, sore throats and acute nephritis. *J R Coll Gen Pract* 1983; **33**: 783-6.
137. Van Buchem FL, Dunk JHM, Vanthof MA. Therapy of Acute Otitis-Media - Myringotomy, Antibiotics, or Neither - a Double-Blind-Study in Children. *Lancet* 1981; **2**: 883-7.
138. van Buchem FL, Knottnerus JA, Schrijnemaekers VJJ et al. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. *Lancet* 1997; **349**: 683-7.
139. Thompson PL, Gilbert RE, Long PF et al. Effect of Antibiotics for Otitis Media on Mastoiditis in Children: A Retrospective Cohort Study Using the United Kingdom General Practice Research Database. *Pediatrics* 2009; **123**: 424-30.
140. Winchester CC, Macfarlane TV, Thomas M et al. Antibiotic Prescribing and Outcomes of Lower Respiratory Tract Infection in UK Primary Care. *Chest* 2009; **135**: 1163-72.
141. Zwart S, Rovers MM, de Melker RA et al. Penicillin for acute sore throat in children: randomised, double blind trial. *Brit Med J* 2003; **327**: 1324-6.
142. Butler CC, Simpson SA, Dunstan F et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* 2012; **344**: d8173.
143. Fernandez Urrusuno R, Pedregal Gonzalez M, Torrecilla Rojas MA. Antibiotic prescribing patterns and hospital admissions with respiratory and urinary tract infections. *Eur J Clin Pharmacol* 2008; **64**: 1005-11.
144. Finnbogadottir AF, Petersen H, Laxdal T et al. An increasing incidence of mastoiditis in children in Iceland. *Scand J Infect Dis* 2009; **41**: 95-8.
145. Groth A, Enoksson F, Hermansson A et al. Acute mastoiditis in children in Sweden 1993-2007--no increase after new guidelines. *Int J Pediatr Otorhinolaryngol* 2011; **75**: 1496-501.
146. Lelorier J, Derderian F. Effect of listing ciprofloxacin in provincial formularies on hospitalizations for bronchitis and pyelonephritis. 1998; **5**: 133-7.
147. Little P, Watson L, Morgan S et al. Antibiotic prescribing and admissions with major suppurative complications of respiratory tract infections: a data linkage study. *Brit J Gen Pract* 2002; **52**: 187-93.

148. Majeed A, Williams S, Jarman B et al. Prescribing of antibiotics and admissions for respiratory tract infections in England. *BMJ* 2004; **329**: 879.
149. Palma S, Rosafio C, Del Giovane C et al. The impact of the Italian guidelines on antibiotic prescription practices for acute otitis media in a paediatric emergency setting. *Ital J Pediatr* 2015; **41**: 37.
150. Price DB, Honeybourne D, Little P et al. Community-acquired pneumonia mortality: a potential link to antibiotic prescribing trends in general practice. *Respir Med* 2004; **98**: 17-24.
151. Sharland M, Kendall H, Yeates D et al. Antibiotic prescribing in general practice and hospital admissions for peritonsillar abscess, mastoiditis, and rheumatic fever in children: time trend analysis (Reprinted). *Clin Otolaryngol* 2005; **30**: 544-5.
152. De Meyere M, Mervielde Y, Verschraegen G et al. Effect of Penicillin on the Clinical Course of Streptococcal Pharyngitis in General-Practice. *Eur J Clin Pharmacol* 1992; **43**: 581-5.
153. Deeks JJ, Dinnes J, D'Amico R et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; **7**: iii-x, 1-173.
154. Cushen R, Francis NA. Antibiotic use and serious complications following acute otitis media and acute sinusitis: a retrospective cohort study. *Brit J Gen Pract* 2020; **70**: E255-E63.
155. Ahovuo-Saloranta A, Borisenko OV, Kovanen N et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev* 2008: CD000243.
156. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Db Syst Rev* 2013.
157. Thomas M, Del Mar C, Glasziou P. How effective are treatments other than antibiotics for acute sore throat? *Br J Gen Pract* 2000; **50**: 817-20.
158. Rosenfeld RM, Singer M, Jones S. Systematic review of antimicrobial therapy in patients with acute rhinosinusitis. *Otolaryngol Head Neck Surg* 2007; **137**: S32-45.
159. Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. *Cochrane Database Syst Rev* 2016; **2**: CD007880.
160. Vouloumanou EK, Karageorgopoulos DE, Kazantzi MS et al. Antibiotics versus placebo or watchful waiting for acute otitis media: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2009; **64**: 16-24.
161. Del Mar C. Managing sore throat: a literature review. II. Do antibiotics confer benefit? *Med J Aust* 1992; **156**: 644-9.
162. Gadomski AM. Potential interventions for preventing pneumonia among young children: lack of effect of antibiotic treatment for upper respiratory infections. *Pediatr Infect Dis J* 1993; **12**: 115-20.
163. Gharbi M, Drysdale JH, Lishman H et al. Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study. *Bmj-Brit Med J* 2019; **364**.
164. Herrett E, Gallagher AM, Bhaskaran K et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**: 827-36.
165. McDonald L, Schultze A, Carroll R et al. Performing studies using the UK Clinical Practice Research Datalink: to link or not to link? *Eur J Epidemiol* 2018; **33**: 601-5.
166. Vezyridis P, Timmons S. Evolution of primary care databases in UK: a scientometric analysis of research output. *BMJ open* 2016; **6**: e012785.
167. Dave S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiol Drug Saf* 2009; **18**: 704-7.
168. Joint Formulary Committee. British National Formulary. London: BMA, RPS: BMJ Group and Pharmaceutical Press, 2015.
169. Brock A, Griffiths C, Rooney C. The impact of introducing ICD-10 on analysis of respiratory mortality trends in England and Wales. *Health Stat Q* 2006: 9-17.

170. Ashworth M, Charlton J, Ballard K et al. Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995-2000. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2005; **55**: 603-8.
171. McKenna HP. The Delphi technique: a worthwhile research approach for nursing? *J Adv Nurs* 1994; **19**: 1221-5.
172. Ashworth M, Latinovic R, Charlton J et al. Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. *J Public Health (Oxf)* 2004; **26**: 268-74.
173. Currie CJ, Berni E, Jenkins-Jones S et al. Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. *BMJ* 2014; **349**: g5493.
174. Gulliford MC, Dregan A, Moore MV et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. *BMJ Open* 2014; **4**: e006245.
175. Hawker JI, Smith S, Smith GE et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. *J Antimicrob Chemoth* 2014; **69**: 3423-30.
176. Thompson PL, Gilbert RE, Long PF et al. Has UK guidance affected general practitioner antibiotic prescribing for otitis media in children? *J Public Health-Uk* 2008; **30**: 479-86.
177. Trotter CL, Stuart JM, George R et al. Increasing hospital admissions for pneumonia, England. *Emerg Infect Dis* 2008; **14**: 727-33.
178. Venekamp RP, Sanders S, Glasziou PP et al. Antibiotics for acute otitis media in children. *Cochrane Db Syst Rev* 2013.
179. National Institue for Health and Care Excellence N. Respiratory tract infections (self-limiting): prescribing antibiotics Clinical guideline [CG69]. Chapter 1 Guidance. https://www.nice.org.uk/guidance/cg69/chapter/1-Guidance2020, date last accessed).
180. Masood A, Moumoulidis I, Panesar J. Acute rhinosinusitis in adults: an update on current management. *Postgrad Med J* 2007; **83**: 402-8.
181. Vincent MT, Celestin N, Hussain AN. Pharyngitis. *Am Fam Physician* 2004; **69**: 1465-70.
182. Sharland M. Manual of Childhood Infections (Oxford Specialist Handbooks in Paediatrics)The Blue Book. In: Sharland MC, A. Shingadia, D., ed, 2011.
183. Pang LHY, Barakate MS, Havas TE. Mastoiditis in a paediatric population: A review of 11 years experience in management. *Int J Pediatr Otorhi* 2009; **73**: 1520-4.
184. Germiller JA, Monin DL, Sparano AM et al. Intracranial complications of sinusitis in children and adolescents and their outcomes. *Arch Otolaryngol* 2006; **132**: 969-76.
185. Lamagni T, Guy R, Chand M et al. Resurgence of scarlet fever in England, 2014-16: a population-based surveillance study. *Lancet Infectious Diseases* 2018; **18**: 180-7.
186. Millett ERC, De Stavola BL, Quint JK et al. Risk factors for hospital admission in the 28days following a community-acquired pneumonia diagnosis in older adults, and their contribution to increasing hospitalisation rates over time: a cohort study. *Bmj Open* 2015; **5**.
187. Munson S, Raluy-Callado M, Lambrelli D et al. Clinical burden of pneumonia, meningitis and septicemia in Norway 2 years after 7-valent pneumococcal conjugate vaccine introduction. *Scand J Public Healt* 2015; **43**: 657-66.
188. Laupland KB, Church DL. Population-Based Epidemiology and Microbiology of Community-Onset Bloodstream Infections. *Clin Microbiol Rev* 2014; **27**: 647-64.
189. Inada-Kim M, Page B, Maqsood I et al. Defining and measuring suspicion of sepsis: an analysis of routine data. *Bmj Open* 2017; **7**.
190. Albaraznji SM, Al Ansari K, Radi MM. Acute mastoiditis in children in the State of Qatar. *Journal of Emergency Medicine, Trauma and Acute Care* 2014: 6.
191. Gunst JD, Jensen-Fangel S, Jespersen B et al. Central nervous system infections among individuals with and without end-stage renal disease. *J Infection* 2013; **67**: 19-26.
192. Wiksten J, Hytonen M, Pitkaranta A et al. Who ends up having tonsillectomy after peritonsillar infection? *Eur Arch Otorhinolaryngol* 2012; **269**: 1281-4.

193. Oliver J, Pierse N, Williamson DA et al. Estimating the likely true changes in rheumatic fever incidence using two data sources. *Epidemiol Infect* 2018; **146**: 265-75.
194. Jackson SJ, Steer AC, Campbell H. Systematic Review: Estimation of global burden of non-suppurative sequelae of upper respiratory tract infection: rheumatic fever and post-streptococcal glomerulonephritis. *Trop Med Int Health* 2011; **16**: 2-11.
195. Muscatello DJ, O'Grady KA, Neville K et al. Acute poststreptococcal glomerulonephritis: public health implications of recent clusters in New South Wales and epidemiology of hospital admissions. *Epidemiol Infect* 2001; **126**: 365-72.
196. Gulmez SE, Holm A, Frederiksen H et al. Use of proton pump inhibitors and the risk of community-acquired pneumonia - A population-based case-control study. *Arch Intern Med* 2007; **167**: 950-5.
197. Saxena S, Atchison C, Cecil E et al. Additive impact of pneumococcal conjugate vaccines on pneumonia and empyema hospital admissions in England. *J Infection* 2015; **71**: 428-36.
198. Barlam TF, Soria-Saucedo R, Cabral HJ et al. Unnecessary Antibiotics for Acute Respiratory Tract Infections: Association With Care Setting and Patient Demographics. *Open Forum Infect Di* 2016; **3**.
199. Gupta R, Crowley S. Increasing paediatric empyema admissions. *Thorax* 2006; **61**: 179-80.
200. Muller-Pebody B, Crowcroft NS, Zambon MC et al. Modelling hospital admissions for lower respiratory tract infections in the elderly in England. *Epidemiol Infect* 2006; **134**: 1150-7.
201. Green CA, Yeates D, Goldacre A et al. Admission to hospital for bronchiolitis in England: trends over five decades, geographical variation and association with perinatal characteristics and subsequent asthma. *Archives of Disease in Childhood* 2016; **101**: 140-6.
202. Millett ERC, Quint JK, Smeeth L et al. Incidence of Community-Acquired Lower Respiratory Tract Infections and Pneumonia among Older Adults in the United Kingdom: A Population-Based Study. *PLoS One* 2013; **8**.
203. Cheng SH, Chen CC, Hou YF. A Longitudinal Examination of Continuity of Care and Avoidable Hospitalization Evidence From a Universal Coverage Health Care System. *Arch Intern Med* 2010; **170**: 1671-7.
204. NHS Digital. Summary Hospital-level Mortality Indicator (SHMI) Indicator specification. https://beta.digital.nhs.uk/binaries/content/documents/corporate-website/publication-system/ci-hub/summary-hospital-level-mortality-indicator-shmi/summary-hospital-level-mortality-indicator-shmi/publicationsystem%3Acilandingasset%5B3%5D/publicationsystem%3AAttachments/publicationsystem%3AattachmentResource2020, date last accessed).
205. Craig P, Cooper C, Gunnell D et al. Using natural experiments to evaluate population health interventions: new Medical Research Council guidance. *J Epidemiol Community Health* 2012; **66**: 1182-6.
206. Shadish WR, Cook TD, Campbell DT. *Experimental and quasi-experimental designs for generalized causal inference*. Boston: Houghton Mifflin, Co., 2002.
207. Schechner V, Temkin E, Harbarth S et al. Epidemiological interpretation of studies examining the effect of antibiotic usage on resistance. *Clin Microbiol Rev* 2013; **26**: 289-307.
208. Pape UJ, Millett C, Lee JT et al. Disentangling secular trends and policy impacts in health studies: use of interrupted time series analysis. *J R Soc Med* 2013; **106**: 124-9.
209. Wagner AK, Soumerai SB, Zhang F et al. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002; **27**: 299-309.
210. Linden A. Challenges to validity in single-group interrupted time series analysis. *J Eval Clin Pract* 2017; **23**: 413-8.
211. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017; **46**: 348-55.
212. Gharbi M, Quenel P, Gustave J et al. Time series analysis of dengue incidence in Guadeloupe, French West Indies: Forecasting models using climate variables as predictors. *Bmc Infect Dis* 2011; **11**.
213. Bhaskaran K, Gasparrini A, Hajat S et al. Time series regression studies in environmental epidemiology. *Int J Epidemiol* 2013; **42**: 1187-95.

214. Helfenstein U. The Use of Transfer-Function Models, Intervention Analysis and Related Time-Series Methods in Epidemiology. *Int J Epidemiol* 1991; **20**: 808-15.
215. Box GEP, Jenkins GM, Reinsel GC et al. *Time series analysis : forecasting and control*. Hoboken, NJ, USA: John Wiley & Sons, Inc., 2016.
216. Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. *Stata J* 2015; **15**: 480-500.
217. Linden A, Adams JL, Roberts N. Evaluating disease management program effectiveness: an introduction to time-series analysis. *Dis Manag* 2003; **6**: 243-55.
218. Lopez Bernal J, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. *J Clin Epidemiol* 2018; **103**: 82-91.
219. McNulty C, Joshi P, Butler CC et al. Have the public's expectations for antibiotics for acute uncomplicated respiratory tract infections changed since the H1N1 influenza pandemic? A qualitative interview and quantitative questionnaire study. *BMJ open* 2012; **2**: e000674.
220. Zakikhany K, Degail MA, Lamagni T et al. Increase in invasive Streptococcus pyogenes and Streptococcus pneumoniae infections in England, December 2010 to January 2011. *Euro Surveill* 2011; **16**.
221. Morris DE, Cleary DW, Clarke SC. Secondary Bacterial Infections Associated with Influenza Pandemics. *Front Microbiol* 2017; **8**: 1041.
222. Reynolds R, Lambert PC, Burton PR et al. Analysis, power and design of antimicrobial resistance surveillance studies, taking account of inter-centre variation and turnover. *J Antimicrob Chemother* 2008; **62 Suppl 2**: ii29-39.
223. Smith DRM, Dolk FCK, Pouwels KB et al. Defining the appropriateness and inappropriateness of antibiotic prescribing in primary care. *J Antimicrob Chemother* 2018; **73**: ii11-ii8.
224. Spivak ES, Cosgrove SE, Srinivasan A. Measuring Appropriate Antimicrobial Use: Attempts at Opening the Black Box. *Clin Infect Dis* 2016; **63**: 1639-44.
225. Committee. JF. British National Formulary. London: BMA, RPS: BMJ Group and Pharmaceutical Press, 2015.
226. Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. *Br J Gen Pract* 2002; **52**: 401-9.
227. Meropol SB, Chen Z, Metlay JP. Reduced antibiotic prescribing for acute respiratory infections in adults and children. *Br J Gen Pract* 2009; **59**: e321-8.
228. Pebody RG, Green HK, Warburton F et al. Significant spike in excess mortality in England in winter 2014/15 - influenza the likely culprit. *Epidemiol Infect* 2018; **146**: 1106-13.
229. Steinman MA, Landefeld CS, Gonzales R. Predictors of broad-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care. *JAMA* 2003; **289**: 719-25.
230. Gerber JS, Prasad PA, Fiks AG et al. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. *JAMA* 2013; **309**: 2345-52.
231. Public Health England P. English surveillance programme antimicrobial utilisation and resistance (ESPAUR): report 2018. https://webarchive.nationalarchives.gov.uk/20191006002348/https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/759975/ESPAUR_2018_report.pdf.
232. Greene RA, Beckman H, Chamberlain J et al. Increasing adherence to a community-based guideline for acute sinusitis through education, physician profiling, and financial incentives. *Am J Manag Care* 2004; **10**: 670-8.
233. Sabuncu E, David J, Bernede-Bauduin C et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. *PLoS Med* 2009; **6**: e1000084.
234. Arrowsmith ME, Majeed A, Lee JT et al. Impact of pay for performance on prescribing of long-acting reversible contraception in primary care: an interrupted time series study. *PLoS One* 2014; **9**: e92205.

235. Serumaga B, Ross-Degnan D, Avery AJ et al. Effect of pay for performance on the management and outcomes of hypertension in the United Kingdom: interrupted time series study. *Bmj-Brit Med J* 2011; **342**.
236. MacBride-Stewart SP, Elton R, Walley T. Do quality incentives change prescribing patterns in primary care? An observational study in Scotland. *Fam Pract* 2008; **25**: 27-32.
237. Bottle A, Millett C, Xie Y et al. Quality of primary care and hospital admissions for diabetes mellitus in England. *J Ambul Care Manage* 2008; **31**: 226-38.
238. Campbell SM, Reeves D, Kontopantelis E et al. Effects of pay for performance on the quality of primary care in England. *N Engl J Med* 2009; **361**: 368-78.
239. Gillam S, Steel N. The Quality and Outcomes Framework-where next? *Bmj-Brit Med J* 2013; **346**: f659.
240. Harrison MJ, Dusheiko M, Sutton M et al. Effect of a national primary care pay for performance scheme on emergency hospital admissions for ambulatory care sensitive conditions: controlled longitudinal study. *Bmj-Brit Med J* 2014; **349**.
241. Ashworth M. Quality and Outcomes Framework: time to take stock. *Brit J Gen Pract* 2010; **60**: 637-8.
242. Ashworth M, Charlton J, Latinovic R et al. Age-related changes in consultations and antibiotic prescribing for acute respiratory infections, 1995-2000. Data from the UK General Practice Research Database. *J Clin Pharm Ther* 2006; **31**: 461-7.
243. Dave S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiol Drug Saf* 2009; **18**: 704-7.
244. Wang Y, Hunt K, Nazareth I et al. Do men consult less than women? An analysis of routinely collected UK general practice data. *BMJ Open* 2013; **3**: e003320.
245. McNulty CA, Nichols T, French DP et al. Expectations for consultations and antibiotics for respiratory tract infection in primary care: the RTI clinical iceberg. *Br J Gen Pract* 2013; **63**: e429-36.
246. Sun XH, Douiri A, Gulliford M. Pneumonia incidence trends in UK primary care from 2002 to 2017: population-based cohort study. *Epidemiol Infect* 2019; **147**.
247. Fry AM, Shay DK, Holman RC et al. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. *Jama-J Am Med Assoc* 2005; **294**: 2712-9.
248. Quan TP, Fawcett NJ, Wrightson JM et al. Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998-2014. *Thorax* 2016; **71**: 535-42.
249. Public Health England. PHE. Guidelines for the public health management of scarlet fever outbreaks in schools, nurseries and other childcare settings. October 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/656687/Guidelines_for_the_public_health_management_of_scarlet_fever_outbreaks__.pdf.
250. Mazzeo F, Mangrella M, Falcone G et al. Antibiotic drug prescription in respiratory tract infections: a pharmacoepidemiological survey among general practitioners in a region of Italy. *J Chemother* 2000; **12**: 153-9.
251. NHS England, Contracting and Incentives Team, Commissioning Strategy. Commissioning for Quality and Innovation (CQUIN). Guidance for 2015/16. https://www.england.nhs.uk/wp-content/uploads/2015/03/9-cquin-guid-2015-16.pdf.
252. Rhee C, Klompas M. Sepsis trends: increasing incidence and decreasing mortality, or changing denominator? *J Thorac Dis* 2020; **12**: S89-S100.
253. CDC CfDCaP. ICD-10-CM Official Guidelines for Coding and Reporting. FY 2017 (October 1, 2016 - September 30, 2017) https://www.cdc.gov/nchs/data/icd/10cmguidelines_2017_final.pdf.
254. Pebody R, Warburton F, Andrews N et al. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. *Euro Surveill* 2015; **20**.
255. Skowronski DM, Chambers C, Sabaiduc S et al. A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014-2015 Season. *Clin Infect Dis* 2016; **63**: 21-32.

256. Nichol KL, Nordin JD, Nelson DB et al. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med* 2007; **357**: 1373-81.
257. Gross PA, Hermogenes AW, Sacks HS et al. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med* 1995; **123**: 518-27.
258. McGivern G, Malcolm W, Marwick C et al. Measuring potential unintended consequences of reducing primary care antibiotic prescribing using NHS Scotland's Infection Intelligence Platform. https://www.isdscotland.org/Health-Topics/Health-and-Social-Community-Care/Infection-Intelligence-Platform/Communications/_docs/20162709_Poster_7b.pdf2020, date last accessed).
259. Gulliford MC, Charlton J, Winter JR et al. Probability of sepsis after infection consultations in primary care in the United Kingdom in 2002-2017: Population-based cohort study and decision analytic model. *Plos Med* 2020; **17**: e1003202.
260. Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied logistic regression*: John Wiley & Sons, 2013.
261. Kirkwood BR, Sterne JA. *Essential medical statistics*: John Wiley & Sons, 2010.
262. Hayhoe B, Greenfield G, Majeed A. Is it getting easier to obtain antibiotics in the UK? *The British journal of general practice : the journal of the Royal College of General Practitioners* 2019; **69**: 54-5.
263. Fowler S, Webber A, Cooper BS et al. Successful use of feedback to improve antibiotic prescribing and reduce Clostridium difficile infection: a controlled interrupted time series. *J Antimicrob Chemoth* 2007; **59**: 990-5.
264. Kwong JC, Maaten S, Upshur REG et al. The Effect of Universal Influenza Immunization on Antibiotic Prescriptions: An Ecological Study. *Clinical Infectious Diseases* 2009; **49**: 750-6.
265. Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. *P Natl Acad Sci USA* 2018; **115**: 12896-901.
266. Lau WCY, Murray M, El-Turki A et al. Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom. *Vaccine* 2015; **33**: 5072-9.
267. Department of Health and Social Care. Tackling AMR 2019-2024. The UK's five-year National Action Plan. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf (01/12/2020 2020, date last accessed).
268. PHE PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). Report 2019 - 2020.
269. Buttery J, Yang Y, Sharland M et al. World Society for Pediatric Infectious Diseases declaration on combating antimicrobial resistance in children. *World J Pediatr* 2018.
270. Scottish Antimicrobial Prescribing Group (SAPG). SAPG Prescribing Indicators Report. Antibacterial Primary Care Prescribing Indicators. Annual Report 2013-14. https://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/SAPG/Prescribing-Indicator-Report/.
271. Hammond A, Stuijfzand B, Avison MB et al. Antimicrobial resistance associations with national primary care antibiotic stewardship policy: Primary care-based, multilevel analytic study. *PLoS One* 2020; **15**.
272. Harbarth S, Balkhy HH, Goossens H et al. Antimicrobial resistance: one world, one fight! *Antimicrob Resist In* 2015; **4**.
273. Rawson TM, Moore LSP, Zhu N et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. *Clin Infect Dis* 2020; **71**: 2459-68.
274. Malcolm W, Seaton RA, Haddock G et al. Impact of the COVID-19 pandemic on community antibiotic prescribing in Scotland. *JAC-Antimicrobial Resistance* 2020; **2**.
275. World Health Organization W. WHO Governing Body Documentation. Official Records. World Health Assembly Resolutions on antimicrobial use and resistance. WHA A51/9 Background and WHA 51.17 Resolution. https://www.who.int/drugresistance/AMR_DC_Resolutions/en/.

276. Shallcross LJ, Davies SC. The World Health Assembly resolution on antimicrobial resistance. *J Antimicrob Chemoth* 2014; **69**: 2883-5.
277. Department of Health and Social Care. Resistance to antibiotics and other antimicrobial agents. Health Service Circular: HSC 1999/049 1999. . https://webarchive.nationalarchives.gov.uk/20120503111150/http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Healthservicecirculars/DH_4016586
278. Department of Health and Social Care. UK antimicrobial resistance strategy and action plan. https://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4007783.
279. World Health Organization W. WHO Global Strategy for Containment of Antimicrobial Resistance. https://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf.
280. World Health Organization W. WHO Governing Body Documentation. Official Records. World Health Assembly Resolutions on antimicrobial use and resistance. WHA A58/14, WHA58.27. https://www.who.int/drugresistance/AMR_DC_Resolutions/en/.
281. One Health Initiative. About the One Health Initiative. http://www.onehealthinitiative.com/about.php.
282. World Health Organization W. WHO Governing Body Documentation. Official Records. World Health Assembly Resolutions on antimicrobial use and resistance. WHA A60/28, WHA 60.16. https://www.who.int/drugresistance/AMR_DC_Resolutions/en/.
283. Simpson SA, Butler CC, Hood K et al. Stemming the Tide of Antibiotic Resistance (STAR): A protocol for a trial of a complex intervention addressing the 'why' and 'how' of appropriate antibiotic prescribing in general practice. *Bmc Fam Pract* 2009; **10**.
284. McNulty CAM, Cookson BD, Lewis MAO. Education of healthcare professionals and the public. *J Antimicrob Chemoth* 2012; **67**: I11-I8.
285. World Health Organization W. WHO Governing Body Documentation. Official Records. World Health Assembly Resolutions on antimicrobial use and resistance. Progress report on 2007 Rational Use of Medicines Resolution. https://www.who.int/drugresistance/AMR_DC_Resolutions/en/.
286. D'Atri F, Arthur J, Blix HS et al. Targets for the reduction of antibiotic use in humans in the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) partner countries. *Eurosurveillance* 2019; **24**: 2-12.
287. World Health Organization W. World Health Day 2011: Policy briefs. https://www.who.int/world-health-day/2011/policybriefs/en/ (16 December 2019.
288. European Commission D-GfHC, . Communication from the Commission to the European Parliament and the Council: Action plan against the rising threats from Antimicrobial Resistance. https://ec.europa.eu/health/amr/sites/amr/files/communication_amr_2011_748_en.pdf.
289. World Health Organization WE. Regional office for Europe. Sixty-first session. Resolution: European strategic action plan on antibiotic resistance. EUR/RC61/R6. http://www.euro.who.int/en/about-us/governance/regional-committee-for-europe/past-sessions/sixty-first-session/documentation/resolutions/eurrc61r6-european-strategic-action-plan-on-antibiotic-resistance (16 December 2019.
290. Council of the European Union. Council Conclusions on the Impact of Antimicrobial Resistance in the Human Health Sector and in the Veterinary Sector—a 'One Health' Perspective. . https://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/131126.pdf.
291. Department of Health and Social Care. Independent report. Chief Medical Officer annual report 2011: antimicrobial resistance. Volume 2. https://www.gov.uk/government/publications/chief-medical-officer-annual-report-volume-22020, date last accessed).
292. The The InterAcademy Partnership (IAP) for Policy and The InterAcademy Medical Panel (IAMP). IAP/IAMP Statement on Antimicrobial Resistance: A Call for Action. http://www.interacademies.org/22719/call_for_action.
293. Foreign & Commonwealth Office. G8 Science Ministers Statement. https://www.gov.uk/government/news/g8-science-ministers-statement.

294. Department of Health and Social Care. Guidance: UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018. https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018.
295. Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI). 6th Annual Report, April 2014 - March 2015. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/707165/ARHAI_annual_report_2014_to_2015.pdf.
296. World Health Organization W. WHO Governing Body Documentation. Official Records. World Health Assembly Resolutions on antimicrobial use and resistance. Resolution: WHA 67.25 - Antimicrobial Resistance. https://www.who.int/drugresistance/AMR_DC_Resolutions/en/.
297. ReAct ARCA, . Antibiotic Resistance Coalition – Civil Society Declaration on Antibiotic Resistance: Declaration on Antibiotic Resistance 22 May 2014. https://www.reactgroup.org/uploads/ARC-declaration/ARC-declaration-May-22-2014.pdf.
298. Global Health Security Agenda (GHSA). Global Health Security Agenda. Antimicrobial Resistance Action Package (GHSA Action Package Prevent-1). https://www.ghsagenda.org/packages/p1-antimicrobial-resistance

https://www.cdc.gov/globalhealth/security/actionpackages/antimicrobial_resistance.htm.
299. World Health Organization W. WHO Governing Body Documentation. Official Records. Resolution: WHA A68/20 - Antimicrobial resistance. Draft global action plan on antimicrobial resistance. https://www.who.int/drugresistance/AMR_DC_Resolutions/en/.
300. World Health Organization W. Global action plan on antimicrobial resistance. World Health Organization. https://apps.who.int/iris/handle/10665/193736.
301. G7 Health Ministers. G7 Summit, Declaration of the G7 Health Ministers 8 - 9 October 2015 in Berlin. Think Ahead, Act Together. http://www.g7.utoronto.ca/healthG8/2015-berlin.pdf.
302. Public Health England P. UK one health report: joint report on human and animal antibiotic use, sales and resistance, 2013. https://www.gov.uk/government/publications/uk-one-health-report-antibiotics-use-in-humans-and-animals.
303. Department of Health and Social Care. The Health and Social Care Act 2008: code of practice on the prevention and control of infections and related guidance. https://www.gov.uk/government/publications/the-health-and-social-care-act-2008-code-of-practice-on-the-prevention-and-control-of-infections-and-related-guidance.
304. News NE. Patient safety alert – addressing antimicrobial resistance through implementation of an antimicrobial stewardship programme. https://www.england.nhs.uk/2015/08/psa-amr/.
305. Public Health England P. English surveillance programme antimicrobial utilisation and resistance (ESPAUR) 2010 to 2014: report 2015. https://webarchive.nationalarchives.gov.uk/20191003132022/https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report.
306. Centers for Disease Control and Prevention C. Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), Actions & Recommendations. https://www.cdc.gov/drugresistance/tatfar/tatfar-recomendations.html.
307. Veterinary Record. G7 nations commit to tackling antimicrobial resistance. *BMJ Journals* 2016; **178**.
308. NHS England. CCG Improvement and Assessment Framework 2016/17. https://www.england.nhs.uk/commissioning/regulation/ccg-assess/.
309. Department of Health and Social Care. Government response to the Review on Antimicrobial Resistance.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/553471/Gov_response_AMR_Review.pdf

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/553471/Gov_response_AMR_Review.pdf.

310. Public Health England P. English surveillance programme antimicrobial utilisation and resistance (ESPAUR): report 2016. https://webarchive.nationalarchives.gov.uk/20191003132022/https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report.
311. G20 Leaders. G20 Leaders´ Declaration: Shaping an interconnected world. . https://www.oecd.org/els/health-systems/G20-leaders-declaration.pdf.
312. OECD W, FAO and OIE. Final note - Tackling Antimicrobial Resistance, Ensuring Sustainable R&D. https://www.oecd.org/els/health-systems/G20-AMR-Final-Paper-2017.pdf.
313. NHS England. CCG Improvement and Assessment Framework 2017/18. https://www.england.nhs.uk/commissioning/regulation/ccg-assess/.
314. Medical Research Council. Antimicrobial Resistance Funders' Forum.
315. Bland JM, Altman DG. Statistics notes - The odds ratio. *Brit Med J* 2000; **320**: 1468-.
316. Schmidt CO, Kohlmann T. When to use the odds ratio or the relative risk? *Int J Public Health* 2008; **53**: 165-7.

APPENDICES

Appendix 1. Intervention timeline details (Chapter 1, Page 1 of 10)

Year	Intervention	Type of intervention	Ref
1998	The first 'World Health Assembly: AMR resolution'. The 51st WHA on Emerging and other communicable disease assembly focused on AMR resolutions.	International: Official text and/or guidance	275, 276
1998	Standing Medical Advisory Committee (SMAC) interdisciplinary sub-group on AMR published a report on an AMR national strategy entitled "The Path to Least Resistance". Report aimed at identifying clinical practices which may predispose to the development of AMR and recommendations to prevent this.	National: Official text and/or guidance	55, 57
1999	Department of Health and Social Care (DH) (then known as Department of Health) responds to the House of Lords Science and Technology Select Committee Report “Resistance to Antibiotics and other Antimicrobial agents” by outlining actions for the NHS to reduce the spread of AMR.	National: Official text and/or guidance	277
1999	DH annual antibiotic awareness campaigns established, aimed at educating healthcare professionals and reducing public expectations of antibiotics for coughs and colds. Campaigns occur annually and predominantly include posters and leaflets distributed to healthcare settings.	National: AMS campaign	55, 75
2000	DH published the first "UK AMR Strategy and Action Plan" providing a UK wide action plan to reduce resistance	National: Official text and/or guidance	55, 278
2001	WHAs on "Revising drug strategy" and "Global health security: epidemic alert and response", with resolutions which included a "WHO medicines strategy"	International: Official text and/or guidance	275, 276
2001	The '2001 WHO Global Strategy for Containment of AMR' was published. This included a global action plan on AMR and a framework of interventions to reduce the emergence of AMR microorganisms.	International: Official text and/or guidance	279
2001	European Surveillance of Antimicrobial Consumption (ESAC) initiated a European-wide data collection of antimicrobial usage, which is analysed and reported on annually	International: Data collection	55

Year	Intervention	Type of intervention	Ref
2003	The Antimicrobial Stewardship subgroup (ASG) of the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) was established and focuses on prudent prescribing of antimicrobials across the NHS; by promoting frameworks and toolkits, defining optimal antimicrobial usage and consumption, using reporting systems and surveillance data, creating assessment tools and improving evidence base for prescribing guidelines.	National: Organisation established	55
2005	WHA on AMR a threat to global health, with resolutions to improve the containment of AMR.	International: Meetings and guidance	276, 280
2006	The One Health Initiative was founded. The initiative promotes a worldwide strategy for expanding interdisciplinary cross-sectoral collaborations and communications in all aspects of health care including interactions of humans, animals and the environment. The initiative champions Global Health Security Action Packages, outputs from the UN General Assembly, implementation of the WHO Global Action Plan, and Food and Agriculture Organisation of the UN and World Organisation for Animal Health (OIE) resolutions.	International: Organisation established	281
2007	WHA progress reports on improving the containment of AMR with Secretariat's report on Rational Use of Medicines.	International: Official text and/or guidance	276, 282
2007	'Stemming the Tide of Antibiotic Resistance' educational programme (STAR) was developed providing resources for primary care clinicians to share and use to communication with the public, as well as availability of educational programmes (online) for clinicians, promoting behaviour change and aiming to reduce inappropriate antibiotic prescribing.	National: AMS resources	283
2008	The UK began participating in European Antibiotic Awareness Day (EAAD, 18th November) activities, which aims to inform patients and healthcare professionals about appropriate antibiotic use and AMR and reinforcing annual awareness internationally through EAAD.	National: AMS campaign	55, 284
2009	WHA progress report on the 2007 Rational Use of Medicines Resolution	International: Meetings and guidance	276, 285
2009	The Antibiotic Stewardship in Primary Care (ASPIC) steering group was established, with the aim of assessing current materials and guidelines to produce a flexible toolkit to be used by prescribers (this has since	National: Organisation established	284

Year	Intervention	Type of intervention	Ref
	been developed: TARGET Antibiotic Toolkit). Key initiatives were to produce: an AMS self-assessment checklist, an interactive antibiotic leaflet for conditions where no- or delayed-antibiotics have been prescribed, and primary care antibiotic guidance.		
2009	Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was created, with CDC as the secretariat. TATFAR unites AMR experts from Canada, the EU, Norway and the U.S to collaborate and share best practice, with AMR work plans and collaborations identified.	International: Organisation established	286
2010	PHE (then known as HPA) published updated antibiotic guidance for primary care clinicians. The guidance would have been modified locally by commissioners prior to practice-level distribution.	National: Official text and/or guidance	55
2010	Antibiotic Resistance and Prescribing in European Children (ARPEC) was launched to improve the quality of community and hospital antibiotic prescribing in children using local and regional data in educational initiatives.	International: Organisation established	55
2011	World Health Day 2011 called for action to combat AMR, with a policy brief and policy package for stakeholders. Package included 6 targets to: commit to a national financed plan with accountability, strengthen surveillance, ensure access to quality medicines, regulate rational use (including in animal husbandry), enhance Infection Prevention and Control, and foster innovation and research and development.	International: Official text and/or guidance	287
2011	The '2011 EU AMR Strategic Action Plan' was published, which specified strategies (with 7 key areas of focus) to progress AMR knowledge and action. This later influenced the development of the UK Five Year Antimicrobial Resistance Strategy 2013-2018. The strategic action plan also focused on supporting fellow European countries in strengthening surveillance and strategies on AMR and was adopted by the Regional Committee for Europe (resolution EUR/RC61/R6).	International: Official text and/or guidance	288, 289
2011	The European Commission established the Joint Programming Initiative on AMR (JPIAMR). A global collaborative organisation for joint planning, implementation and evaluation of national research programmes, consisting of 28 nations with a One Health approach.	International: Organisation established	https://www.jpiamr.eu/
2012	The '2012 EU Council Conclusions' was published by the Council of the European Union, informing on the impact of AMR in the human health sector and the veterinary sector, a "One Health" perspective. The document recalls the council's conclusions from previous years on AMR:	International: Official text and/or guidance	290

Year	Intervention	Type of intervention	Ref
	innovate incentives for effective antibiotics and the assess impact of resistance in the veterinary sector. The report calls on the commission to facilitate the member states to develop, assess and implement national action plans against AMR.		
2012	'Quality, Innovation, Productivity and Prevention' (QIPP) is a large-scale transformational programme for the NHS developed to improve the quality of care the NHS delivers whilst making efficiency savings. QIPP contained measures relating to the choice and usage of antibiotics in England, including a focus on reducing overall antibiotics, cephalosporins and quinolones. Recommendation for shorter duration (3-day course) of antibiotic use for uncomplicated urinary tract infections was also included.	National: AMS programme	
2012	PHE and the DH developed specific antimicrobial prescribing toolkits for primary (Treat Antibiotic Responsibly, Guidance, Education, Tools [TARGET]) and secondary (Start Smart Then focus) care. The resources, hosted on the Royal College of General Practitioners website, were designed to influence perceived barriers and attitudes of patients and prescribers to encourage optimal antibiotic prescribing.	National: AMS resources	[25]
2013	The second volume of the Chief Medical Officer's (CMO), Dame Sally Davies, 2011 annual report was published. This was the first of a thematic annual reporting with the specific field of health and disease being infectious diseases, and a focus on AMR. The report on Infections and the Rise of AMR stated the need for the UK to prioritise AMR as a major area of concern, including it on the national risk register, and pushing for international action. 4 recommendations were made, pertaining to: AMR, surveillance, prevention and education and training of health and care workforce.	National: Official text and/or guidance	[11, 54, 291]
2013	Statement of the Academies of Science: The Global Network of Science Academies and the InterAcademy Medical Panel (IAMP) issued a Joint statement on "Antimicrobial Resistance: A call for Action". Among the recommendations was a call to include AMR in the global sustainable development agenda and the promotion of integrated world-wide surveillance systems and educational programmes that should include human and animal antibiotic use ("One health").	International: Official text and/or guidance	[292]

Year	Intervention	Type of intervention	Ref
2013	G8 Science Ministers and national science academies declaration. The meeting was used to discuss how to promote coherent and coordinated global scientific research and how to address global challenges, with a focus on AMR. Commitments were made for open scientific research data, access internationally to research results and the promotion of a framework for information exchange.	International: Meetings and guidance	293
2013	A cross-government 'UK Five Year Antimicrobial Resistance Strategy 2013-2018' was published, stimulating national and international action. The report included 7 key areas underpinning 3 strategic aims: to improve AMR knowledge and understanding, improve stewardship and effectiveness of existing antibiotics, and stimulate development of new antibiotics/novel therapies and diagnostics.	National: Official text and/or guidance	25, 54, 294
2013	The Strategic and Technical Advisory Group on AMR (STAG-AMR) was convened by the WHO, chaired by Dame Sally Davies. The first meeting of the group was held to help shape a global strategy to tackle AMR and to advise WHO on the organisation's coordination role and priority activities to tackle AMR.	International: Organisation established	https://www.who.int/antimicrobial-resistance/events/stag/en/
2014	ARHAI, the national expert's advisory group on AMR and HCAI, developed antimicrobial prescribing quality measures (APQM) to improve the quality of antimicrobial prescribing in primary and secondary care, with quality measures to reduce total antibiotic prescribing and encourage the use of more narrow spectrum antibiotics. These measures were later used to inform development of the NHS England Quality Premium 2015/16.	National: AMS programme	295
2014	Two National Institute of Health Research Health Protection Research Units (NIHR HPRUs) established with particular focus on HCAI & AMR. These units are a collaboration between universities (Imperial College London and University of Oxford) and PHE and fund high quality research to enhance PHE's ability to protect the public's health and minimise health impact emergencies.	National: Organisation established	https://www.nihr.ac.uk/news/587-million-funding-boost-for-research-to-

Year	Intervention	Type of intervention	Ref
			protect-the-health-of-the-nation/23835
2014	67th WHA: resolution on AMR (WHA 67.25) ratified. There was not wide engagement since the WHO publication of the global action plan in 2001. This WHA meeting provided WHO the mandate to develop and coordinate the global AMR action plan with overarching goals of reducing development of resistance with focused activities around improving AMR knowledge, stewardship of existing treatments and stimulating development of new antibiotics, diagnostics and novel therapies.	International: Official text and/or guidance	296
2014	Antibiotic Resistance Coalition (ARC; represents government, industry and educational societies internationally) declaration to curb excessive antibiotic use whilst ensuring access for those in need, promoting the innovation of systems for new antibiotics and development of diagnostic tools and techniques, and tackling non-human use of antibiotics in food and agriculture were also a priority.	International: Official text and/or guidance	297
2014	CMO nudge letter sent to top 20% antibiotic prescribing GPs, coinciding with winter seasonal increase in antibiotic prescribing. GPs were informed that they were higher prescribers then local peers, were provided with a leaflet to use with patients and given 3 actions to reduce prescribing: advising patients on self-care, offering delayed prescription, speaking with other prescribers at the practice.	National: selective AMS programme	81
2014	ESPAUR launched the Antibiotic Guardian online pledge and resource website (www.antibiotic guardian.com) on the European Antibiotic Awareness Day (EAAD). This was aimed at improved public and professional awareness and engagement in actions to improve antibiotic use.	National: AMS programme	https://antibioticguardian.com/
2014	AMR UK Action Package within the Global Health Security Agenda (GHSA). The GHSA, launched in 2014, is a 67 country collective action to strengthen abilities in preventing, detecting and responding to infectious diseases globally. To encourage progress "Action Packages" were developed to facilitate regional and global collaboration towards	International: Official text and/or guidance	298

Year	Intervention	Type of intervention	Ref
	specific targets. The UK committed to contribute and implement the Action packages, with the first Action package being to prevent AMR (GHSA Action Package Prevent - 1).		
2015	NHS England Quality Premiums (QP) were published to incentivise CCGs in England to improve antibiotic prescribing quality in primary and secondary care: by reducing total inappropriate antibiotic prescribing and the use of broad-spectrum antibiotic use in primary care, and validating prescribing data in secondary care.	National: AMS programme	64
2015	NHS England National Workshops: 3 workshops organised post QP that were attended by approximately 75% CCGs. The workshops were designed to support the implementation of the QP by raising awareness of AMR, promoting AMS activities and toolkits and sharing examples of success within primary care.	National: AMS programme	25
2015	68th WHA: the AMR section included a draft global action plan on AMR. This included advice from the Strategic and Technical Advisory Group (STAG) on AMR.	International: Official text and/or guidance	299
2015	Global action plan on antimicrobial resistance was published by the WHO, declaring AMR a global priority.	International: Official text and/or guidance	300
2015	The 41st G7 summit, Elmau, Bavaria: declaration of G7 Health Ministers. The Berlin Declaration on Antimicrobial Resistance: A Global Union for Antibiotics Research and Development (GUARD) was agreed. The declaration recognizes antimicrobial resistance (AMR) as a serious global threat to public health that requires immediate concerted global action.	International: Meetings and guidance	301
2015	The PHE led "UK one health report: antibiotics use in humans and animals" was published, reporting on antibiotic use, sales and resistance in animals and humans in the UK in 2013.	National: Official text and/or guidance	302
2015	A revised Health and Social care Act 2008, Code of Practice on the Prevention and Control of Infection was published since the 2010 predecessor. This clarified guidance and recommendations around infection, prevention and control (IPC) and antimicrobial stewardship for health care providers, in both primary and secondary care	National: Official text and/or guidance	303
2015	National Institute for Health and Care Excellence (NICE) published guidance on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. This outlined evidence based best	National: Official text and/or guidance	53

Year	Intervention	Type of intervention	Ref
	practice, quality standards and audit tools to aid local action plans and self-assessments.		
2015	National patient safety alert was issued by NHS England, Health Education England and PHE, to highlight the challenges of AMR and the need to implement antimicrobial stewardship. The alert signposted NHS organisations to the TARGET and the Start Smart then Focus toolkits.	National: Official text and/or guidance	[304]
2015	WHO Global Antimicrobial Resistance Surveillance System (GLASS) launched. GLASS was developed to support the global action plan on AMR, supporting global surveillance and research, with 40+ countries enrolled and 20+ reporting.	International: Organisation established	https://www.who.int/glass/en/
2015	ESPAUR published the second report from the programme, containing details of antibiotic prescribing/consumption and resistance trends from 2010 to 2014.	National: Official text and/or guidance	[305]
2015	TATFAR revised AMR transatlantic actions plans for continued collaboration with actions for 2016 through 2020 to be implemented.	International: Official text and/or guidance	[306]
2016	QP2: NHS England update of the QP incentives a further reduction in antibiotic prescribing, with the entire 10% now focused on primary care prescribing.	National: AMS programme	[65]
2016	The Antimicrobial Resistance (AMR) Review was commissioned by the UK Government in 2014 and published in 2016, chaired by Lord Jim O'Neill. This provided estimates of the global burden and cost of AMR if the rise in resistance were to continue, the report also reviewed the role of rapid diagnostics, the pipeline of new antibiotics, the role of agriculture, vaccines and alternative therapies.	National: Official text and/or guidance	[5, 21]
2016	The 42nd G7 summit, ISe-Shima Japan: UK Prime Minister, alongside other leaders announced plans to tackle AMR, and committed to taking action to promote the One Health approach.G7 is an international intergovernmental economic organisation consisting of the seven countries with the largest advanced economies in the world (Canada, France, Germany, Italy, Japan, the UK, and the US.	International: Meetings and guidance	[307]
2016	CCG Improvement and Assurance Framework (IAF), under the Better Health theme, has an indicator encouraging improvement in appropriate antibiotic prescribing in primary care. Assessment of progress is sourced from the QP monitoring dashboard.	National: AMS programme	[308]

Year	Intervention	Type of intervention	Ref
2016	The Government's response to the Review on Antimicrobial Resistance was published. Committed to better use of existing antibiotics and vaccines, innovation of rapid point-of-care diagnostics, global innovation fund to reinvigorate R&D, global surveillance, reducing antimicrobial use in agriculture.	National: Official text and/or guidance	21, 309
2016	ESPAUR published the third annual report (ESPAUR report 2016) highlighting resources and areas of improvement in primary (improving their systems and monitoring) and secondary (focus on post prescribing reviews) care.	National: Official text and/or guidance	310
2016	Primary care prescribing data publicly available on the PHE fingertips AMR Local Indicators (2012-2016).	National: AMS resources	https://fingertips.phe.org.uk/profile/amr-local-indicators
2017	QP3: 2017-19: NHS England update of the QP incentives with part b and c relating to the primary care setting: reducing inappropriate prescribing for UTIs and reducing gram negative bloodstream infections.	National: AMS programme	66
2017	EU G20 Leaders declaration and G20 Health minister meeting. Documentations highlight the importance of implementing National Actions Plans and fostering AMR R&D, particularly for priority pathogens identified by WHO, with a call for a collaboration hub to maximise impact of existing and new antimicrobials.	International: Meetings and guidance	311, 312
2017	ESPAUR's fourth report was published, highlighting the yearly increase in the burden of antibiotic resistant gram-negative bloodstream infections and urinary tract infections, with the majority of samples taken in the community healthcare settings. The report documented a 5% decrease in antibiotic prescribing between 2012 and 2016.	National: Official text and/or guidance	71
2017	CCG Improvement and Assurance Framework (IAF) AMR indicator reinstated in new guidelines, with appropriate primary care prescribing of antibiotics and broad-spectrum antibiotics reinstated as an indicator for improvement.	National: AMS programme	313

Year	Intervention	Type of intervention	Ref
2018	Antimicrobial Resistance Funders' Forum (AMRFF) was established, led by the Medical Research Council (MRC), to provide a forum for sharing information on AMR activities by various member organisations (key funders and stakeholders supporting UK AMR research).	National: Organisation established	[314]

	Ovid MEDLINE® (1946 to search date) search strategy	
#	Searches	Results
1	exp Anti-Bacterial Agents/	613096
2	antibiotic*.tw.	264484
3	1 or 2	725625
4	exp Respiratory Tract Infections/	324970
5	exp Pharyngitis/	14565
7	exp Bronchitis/	28303
8	exp Sinusitis/	18248
9	exp earache/ or exp otitis externa/ or exp otitis media/	25286
10	(sore throat or chest infection* or bronchit* or sinusit* or pharyngit* or rhinit* or rhinosinusit* or tonsillit* or laryngit* or croup* or laryngotracheobronchit* or nasopharyngit* or rhinopharyngit* or tracheit* or whooping or pertussis or cough* or coryza* or otitis* or bronchit* or bronchiolit* or pneumon* or pluerisy or otitis* or earache* or respiratory tract infection*).tw.	1637050
11	4 or 5 or 6 or 7 or 8 or 9 or 10	1929582
12	(primary care or family practi* or general practi* or hospital admission*).tw.	177969
13	(consequence* or sequela or complication* or secondary infection* or incidence or reattend* or re-attend* or mortality or death).tw.	2335418
14	3 and 11 and 12 and 13	847

	Embase Classic + EMBASE (1947 to search date)	
#	Search terms	Results
1	exp antibiotic agent/	1195416
2	antibiotic*.tw	371361
3	1 or 2	1308957
4	exp Respiratory Tract Infections/	393966
5	exp Pharyngitis/	25773
7	exp Bronchitis/	62513
8	exp Sinusitis/	38459
9	exp otitis externa/ or exp otitis media/	38498
10	(sore throat or chest infection* or bronchit* or sinusit* or pharyngit* or rhinit* or rhinosinusit* or tonsillit* or laryngit* or croup* or laryngotracheobronchit* or nasopharyngit* or rhinopharyngit* or tracheit* or whooping or pertussis or cough* or coryza* or otitis* or bronchit* or bronchiolit* or pneumon* or pluerisy or otitis* or earache* or respiratory tract infection*).tw.	2095107
11	4 or 5 or 6 or 7 or 8 or 9 or 10	2548288
12	(primary care or family practi* or general practi* or hospital admission*).tw.	234853
13	(consequence* or sequela or complication* or secondary infection* or incidence or reattend* or re-attend* or mortality or death).tw.	3258377
14	3 and 11 and 12 and 13	1812

	CENTRAL: Issue 7 of 12, July 2016	
#	Searches	Results
1	MeSH descriptor: [Anti-Bacterial Agents] explode all trees	10214
2	antibiotic*	21026
3	#1 or #2	26105
4	MeSH descriptor: [Respiratory Tract Infections] explode all trees	10890
5	MeSH descriptor: [Otitis Media] explode all trees	1112
6	MeSH descriptor: [Otitis Externa] explode all trees	75
7	sore throat or chest infection* or bronchit* or sinusit* or pharyngit* or rhinit* or rhinosinusit* or tonsillit* or laryngit* or croup* or laryngotracheobronchit* or nasopharyngit* or rhinopharyngit* or tracheit* or whooping or pertussis or cough* or coryza* or otitis* or bronchit* or bronchiolit* or pneumon* or pluerisy or otitis* or earache* or respiratory tract infection*	108366
8	#4 or #5 or #6 or #7	118695
9	primary care or family practi* or general practi* or hospital admission*	71882
10	complication* or secondary infection* or incidence or reattend* or re-attend* or mortality	205802
11	#3 and #8 and #9 and #10	2407
12	Trials - CENTRAL	521

	OpenGrey (Previously: system for information on Grey Literature in Europe [SIGLE])	
#	Searches	Results
1	antibiotic* AND ("sore throat" OR "chest infection" or "chest infections" OR bronchit* OR sinusit* OR pharyngit* OR rhinit* OR rhinosinusit* OR tonsillit* OR laryngit* OR croup* OR laryngotracheobronchit* OR nasopharyngit* OR rhinopharyngit* OR tracheit* OR whooping OR pertussis OR cough* OR flu* OR influenza* OR coryza* OR otitis* OR bronchit* OR bronchiolit* OR pneumon* OR pluerisy OR common cold OR otitis* OR earache* OR respiratory OR RTI*)	441

The Study ID, Reviewer ID and date of completion of eligibility for each study, was systematically recorded alongside the screening record on the software used (Eppi-Reviewer 4).

1. Does the paper contain original research and quantitative data? (I.e. is a primary study and not a systematic review, discussion paper, guidance/standards related documents, case report, qualitative study etc.)
    - ☐ Yes: Go to question 2
    - ☐ No: Exclude Paper

2. Does the study investigate patients who have had an uncomplicated respiratory tract infection?
    - ☐ Yes – Go to question 3
    - ☐ No: Exclude paper

3. Does the study investigate the influence of antibiotic prescribing? I.e. the reduction (ecological study) or the absence of antibiotic prescribing (patient-level study).
   (i.e. exclude studies which are comparing the effectiveness of different antibiotics rather than the effect of the use of antibiotics/drug reviews).
    - ☐ Yes – Go to question 4
    - ☐ No: Exclude paper

4. Does the study measure the occurrence of a serious infection/complication which would have developed following an index RTI? I.e. infectious complications rather than progression of symptoms were captured.
    - ☐ Yes – Go to question 5
    - ☐ No: Exclude paper

5. Was the occurrence of a more serious infection related to the reduction (ecological study) or absence of timely antibiotic prescription (patient-level study)? I.e. infectious complications were related to the lack/reduction of antibiotic treatment rather than the use of (e.g. unnecessary/overprescribing may cause diarrhoea due to *Clostridium difficile* infection, skin rash and vomiting).
    - ☐ Yes: Go to question 6
    - ☐ No: Exclude paper

6. If the study is hospital-based, are the antibiotics being investigated related to antibiotics which would be commonly prescribed in primary care, for infections commonly treated for in primary care?
   (i.e. exclude studies which prescribe for progressed infections in secondary care and not related to an uncomplicated index RTI).
    - ☐ Yes – Proceed to data extraction form
    - ☐ No: Exclude paper

Appendix 4. Systematic review data extraction list of variables collected from all included studies (Chapter 2, Page 1 of 2)

	Data variable	Description
Study identification details	Study ID	Unique number assigned to each study. (Systematically produced on Eppi-Reviewer)
	Author	First author of the paper. (Systematically produced on Eppi-Reviewer)
	Year	Year of publication
Study characteristics	Language	Publication language (English or Other [specified])
	Country	Country where the study was conducted
	Primary aim	The studies primary aim
	Study design	Options include: retrospective cohort, prospective cohort, case-control, cross-sectional, Randomised Controlled Trial, Controlled before and after, Interrupted Time Series/Time trend, Other (specify)
	Recruitment time period	Time period during which participants were recruited into study. i.e. start and end dates
	Number of study participants	Total number of participants included in the study. Where applicable, total number of participants allocated to each group assessed e.g. placebo and antibiotic group/ exposed and non-exposed.
	Participants	Brief description of the study participant characteristics, including details of initial index RTI indication
	Study setting	Where participants were recruited from i.e. primary care practice, outpatients etc.
	Recruitment	How participants were recruited into the study; the source and method of participant selection/inclusion/case ascertainment.
	Distinguished bacterial aetiology	Used to identify whether the study participants were patients who had a confirmed bacterial primary infection or were recruited based on general RTI symptoms in primary care (i.e. potential viral aetiology)? (If confirmed these would not be representative of general symptomatic patients who visit the GP)
	Excluded participants/criteria	Exclusion criteria of the study recruitment
	Age range	Age range of study population included in the study and description of age groups assessed, if any (adult/children/elderly/general population, including age bracket where known)

Intervention/ exposure	Intervention details (Ecological studies)	Required for ecological studies. The type of intervention used and the delivery of the intervention: including timing, stages (sequential or simultaneous), frequency, duration etc. Details of the intervention conditions, treatment arms
	Antibiotic, dose and usage (Patient-level studies)	Name of the antibiotic for which exposure was measured and what comparator was used, if any. The dose and usage (e.g. 300mg, three times a day)
	Duration of treatment	Where stated (i.e. patient-level studies) details of duration of antibiotic treatment recorded (e.g. 7 days), multiple antibiotics and antibiotic exposure time period could have been imputed
Observations/ Outcomes	Data collection tool	Data collection method, included options (with further detail required): Observation, primary care consultation; Observation, hospital admission/specialist observation; Self-reported (e.g. diary, questionnaire); Telephone follow-up; Clinical test; Database source
	Infectious complication	List the complications/outcomes which were assessed and reported in the study
	Length of follow-up	Duration of time between exposure (e.g. initial consultation) and outcome measured in the study i.e. how many days/months were the patients followed-up and the frequency of follow-up
	Key study observations	Key findings and conclusions from the study. This included, where stated, the duration of symptoms/primary infection to outcome/hospital admission/mortality (i.e. what was the occurrence of progression of infection related to the intervention e.g. counts of unintended outcomes pre- and post- intervention or in placebo and intervention group) , severity of outcomes, effect size if reported
	Missing data/Loss to follow-up	Indication of the number of participants with missing data (in the total sample and within any groups) or those lost to follow-up (withdrawals/ dropouts/ exclusions)
	Limitations	Limitations of the study, including sources of potential bias or imprecision, this includes the direction/magnitude of potential bias
	Unit of analysis	Whether individual-level or ecological-level study
	Crude odds ratio	Crude odds ratio reported (if data available)
	Crude confidence intervals	Crude confidence intervals reported (if data available)
	Adjusted odds ratio	Adjusted odds ratio (if reported)
	Adjusted confidence intervals	Adjusted confidence intervals (if reported)
	Raw data	Extracted numbers of complications reported, frequency and severity of unintended consequences (i.e. number of events and the number of no events in the exposed and unexposed groups, no antibiotics Vs antibiotics groups, where the information was available)

Appendix 5. Systematic review Critical appraisal Skills Programme (CASP) study quality checklist for Cohort studies, with additional support for reviewer's judgement and identification of bias (Chapter 2, Page 1 of 4)

#	Domain	Support for judgement	Reviewer's judgement	Options	Bias
	Are the results of the study valid?				
1a)	Did the study address a clearly focused issue?	A question can be 'focused' In terms of · The population studied · The risk factors studied · The outcomes considered · Is it clear whether the study tried to detect a beneficial or harmful effect?	Screening	Yes Unclear No	
1b)	Was the study primary outcome to address the issue of focus in this review (unintended consequences)?	Were the primary aims of the study to identify unintended consequences?	Screening	Yes Unclear No	
2	Was the cohort recruited in an acceptable way?	Look for selection bias which might compromise the generalisability of the findings: · Was the cohort representative of a defined population? · Was there something special about the cohort? · Was everybody included who should have been included? · State whether this is a retrospective cohort and whether knowledge of outcomes may have impacted on selection/recruitment.	Selection bias due to concerns of comparability of cohort with the population, and between exposed/unexposed groups.	Yes Unclear No	Selection bias

3	Was the exposure accurately measured to minimise bias?	Look for measurement or classification bias: · Did they use subjective or objective measurements? · Do the measurements truly reflect what you want them to (have they been validated)? · Were all the subjects classified into exposure groups using the same procedure	Measurement/classification/detection bias due to incorrect assessment of outcomes.	Yes Unclear No	Detection bias
4a)	Was the outcome accurately measured to minimise bias? - based on the measurement	Look for measurement or classification bias: · Did they use subjective or objective measurements? · Do the measures truly reflect what you want them to (have they been validated)? · Has a reliable system been established for detecting all the cases (for measuring disease occurrence)? · Were the measurement methods similar in the different groups?	Measurement/classification/detection bias due to incorrect assessment of outcomes.	Yes Unclear No	Detection bias
4b)	Was the outcome accurately measured to minimise bias? - based on blinding of outcome assessment	Look for performance bias: · Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?	Performance bias due to lack of blinding of participants and healthcare providers.	Yes Unclear No	Performance bias
5a)	Have the authors identified all important confounding factors?	Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors. Has the study: (i) restricted participant selection so that all groups had the same value for the confounder; (ii) demonstrated balance between groups for the confounder; (iii) matched on the confounder; or (iv) adjusted for the confounder in statistical analyses to quantify the effect size.	Results did not adjust or take into account confounding factors in study design or analysis.	(List what the authors may have missed, which are of importance.) Yes Unclear No	Misclassification/ Information bias
5b)	Have they taken account of the confounding factors in the design and/or analysis?			Yes Unclear No	

6a)	Was the follow up of subjects complete enough? Were there differences in the participants lost to follow up?	Consider · The persons that are lost to follow-up may have different outcomes than those available for assessment · In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?		Yes Unclear No	Misclassification/ Information bias
6b)	Was the follow up of subjects long enough?	Consider · The good or bad effects should have had long enough to reveal themselves		Yes Unclear No	Misclassification/ Information bias
	What are the results?				
7	Was the outcome data relatively complete? i.e. Attrition and exclusions from the analysis.	State whether attrition and exclusions were reported, the numbers in each group (exposed and unexposed), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.	Yes Unclear No	Attrition bias
	What are the results of this study?	Consider · What are the bottom line results? · Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference? · How strong is the association between exposure and outcome (RR,)? · What is the absolute risk reduction (ARR)?		Data already extracted	
	How precise are the results?	Look for the range of the confidence intervals, if given		Data already extracted	
8a)	There is minimal possibility of selective outcome reporting?	Consider whether · The unintended consequences captured are representative of complete and reliable findings. · The results are unlikely to be report missing or partial unintended consequence, all cases are likely to have been captured.	Reporting bias due to selective reporting of results.	Yes Unclear No	Reporting bias

8b)	Do you believe the results?	Consider · Big effect is hard to ignore · Can it be due to bias, chance or confounding? · Are the design and methods of this study sufficiently flawed to make the results unreliable? · Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)		Yes Unclear No	Other sources of bias
	Will the results help locally?				
9	Can the results be applied to the local population?	Consider whether · A cohort study was the appropriate method to answer this question · The subjects covered in this study could be sufficiently different from your population to cause concern · Your local setting is likely to differ much from that of the study · You can quantify the local benefits and harms		Yes Unclear No	Generalisability
10	Do the results of this study fit with other available evidence?	Consider all the available evidence from RCT's, systematic reviews, cohort studies and case-control studies as well for consistency.		Yes Unclear No	Consistency
11	What are the implications of this study for practice?	Consider · One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making · For certain questions observational studies provide the only evidence · Recommendations from observational studies are always stronger when supported by other evidence		Not collecting	

Appendix 6. Systematic review Critical appraisal Skills Programme (CASP) study quality checklist for Case-control studies (Chapter 2, Page 1 of 5)

#	Domain	Support for judgement	Reviewers' judgement	Options	Bias
	Are the results of the study valid?				
1a)	Did the study address a clearly focused issue?	A question can be 'focused' In terms of · The population studied · The risk factors studied · The outcomes considered · Is it clear whether the study tried to detect a beneficial or harmful effect?	Screening	Yes Unclear No	
1b)	Was the study primary outcome to address the issue of focus in this review (unintended consequences)?	Were the primary aims of the study to identify unintended consequences related to antibiotic use? i.e. in keeping with the review.	Screening	Yes Unclear No	
2	Did the author use an appropriate method to answer their question?	Consider: · Is a case control study an appropriate way of answering the question under the circumstances? (Is the outcome rare or harmful) · Did it address the study question?	Screening	Yes Unclear No	

3	Were the cases recruited in an acceptable way?	Look for selection bias which might compromise the validity of the findings: · Are the cases defined precisely? · Were the cases representative of a defined population? (geographically and/or temporally?) what was the source of cases? · Was there an established reliable system for selecting all the cases? · Are they incident or prevalent? · Is there something special about the cases? · Is the time frame of the study relevant to disease/exposure? · Was there a sufficient number of cases selected? · Was there a power calculation?	Selection bias due to cases being unrepresentative of the population that produced the cases and concerns of comparability of cases to the controls and to the population. Recall bias: The use of incident cases is considered as preferential to prevalent cases, as the recall of past exposure(s) may be more accurate among newly diagnosed cases. The temporal sequence of exposure and disease is easier to assess among incident rather than prevalent cases.	Yes Unclear No	Selection bias
4	Were the controls selected in an acceptable way?	Look for selection bias which might compromise the generalisability of the findings: · Were the controls representative of defined population (geographically and/or temporally) · Was there something special about the controls? · Was the non-response high? Could non-respondents be different in any way? · Are they matched, population based or randomly selected? Is the source of controls the same as that of cases? · Was there a sufficient number of controls selected?	Selection bias due to concerns of generalisability. Selection bias due to controls being unrepresentative of the population that produced the cases and concerns of comparability of controls to the population. Recruitment from an institute that provides healthcare could lead to estimates of the exposure among controls being different from that in the reference population; biased estimates of the association between exposure and disease. Recruiting more than one control per case is thought to improve the statistical power of the study, however including more than 4 controls per case is not thought to be more efficient.	Yes Unclear No	Selection bias

5a)	Was the exposure accurately measured to minimise bias? - based on measurement	Look for measurement, recall or classification bias: · Was the exposure clearly defined and accurately measured? · Did the authors use subjective or objective measurements? · Do the measures truly reflect what they are supposed to measure? (Have they been validated?) · Were the measurement methods similar in the cases and controls? · Is the temporal relation correct? (Does the exposure of interest precede the outcome?)	Measurement/classification/detection/recall bias due to incorrect assessment of exposures.	Yes Unclear No	Measurement/ classification/ detection/ recall bias
5b)	Was the exposure accurately measured to minimise bias? - based on blinding of exposure assessment	Look for interviewer/observer/reporting bias: · Did the study incorporate blinding where feasible?	Interviewer/observer/reporting bias: due to lack of blinding of healthcare providers. Prevalent cases/retrospective nature of design: the recording of exposure information may vary depending on the investigator's knowledge of an individual's disease status. Recall bias where participants are not blinded.	Yes Unclear No	Observer/ recall bias
6a)	What confounding factors have the authors accounted for?	List the confounders that the authors may have missed which are important; i.e. Genetic, environmental, socio-economic factors.	Results did not adjust or take into account confounding factors in study design or analysis.	(List what the authors may have missed, which are of importance.) Yes Unclear No	Misclassification/ Information bias

6b)	Have they taken account of the confounding factors in the design and/or analysis?	Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors. Has the study: (i) restricted participant selection so that all groups had the same value for the confounder; (ii) demonstrated balance between groups for the confounder; (iii) matched on the confounder; or (iv) adjusted for the confounder in statistical analyses to quantify the effect size.	Results did not adjust or consider confounding factors in study design or analysis.	Yes Unclear No	Misclassification/ Information bias
	What are the results?				
	What are the results of this study?	Consider · What are the bottom line results? · Is the analysis appropriate to the design? · How strong is the association between exposure and outcome (look at the odds ratio)? · Are the results adjusted for confounding, and might confounding still explain the association? · Has adjustment made a big difference to the OR?		Data already extracted	
7	How precise are the results? How precise is the estimate of risk?	Consider · Size of the P-value · Size of the confidence intervals · Have the authors considered all the important variables? · How was the effect of subjects refusing to participate evaluated?	Selection bias: are certain groups of participants refusing to participate?	Parts of the data already extracted Yes Unclear No	Selection bias

8	Do you believe the results?	Consider · Big effect is hard to ignore · Can it be due to bias, chance or confounding? · Are the design and methods of this study sufficiently flawed to make the results unreliable? · Bradford Hills criteria (e.g. time sequence, dose-response gradient, strength, biological plausibility, consistency)		Yes Unclear No	Other sources of bias
	Will the results help locally?				
9	Can the results be applied to the local population?	Consider whether · The subjects covered in the study could be sufficiently different from your population to cause concern · Your local setting is likely to differ much from that of the study · Can you quantify the local benefits and harms?		Yes Unclear No	Generalisability
10	Do the results of this study fit with other available evidence?	Consider all the available evidence from RCT's, systematic reviews, cohort studies and case-control studies as well for consistency.		Yes Unclear No	Consistency

Domain	Support for judgement	Reviewer's judgement	Options
Selection bias			
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.	Low risk High risk Unclear
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	Low risk High risk Unclear
Performance bias			
Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Low risk High risk Unclear
Adherence	If adherence is poor within both treatment groups, the difference between groups would be underestimated. If adherence varies by treatment group, the difference between groups may be overestimated. Use of concomitant treatments by both groups can mask the difference between them. Deviation from the study protocol can reduce the sensitivity of a trial. Both can lead to an underestimate of the difference between groups.	Performance bias due to poor adherence with the intervention; reduced sensitivity of the trial either by the participants, or by treatments provided where there is deviation from the study protocol.	Low risk High risk Unclear
Detection bias			
Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Low risk High risk Unclear

Outcome measurement technique	Use of nonvalid instruments or improper use of valid instruments to measure outcomes could lead to an underestimate or overestimate of the difference between groups. Was the duration of treatment long enough in the study? Realistic opportunity for the progression of infection to occur? Or was there misclassification/detection bias?	Detection bias due to outcomes being measured with a non-validated instrument/not objectively measured/the measure was not properly administered.	Low risk High risk Unclear
Attrition bias			
Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.	Low risk High risk Unclear
Reporting bias			
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found. Ideally should include intention-to-treat and per-protocol data, as there could be a bias in favour of treatment or vice versa.	Reporting bias due to selective outcome reporting.	Low risk High risk Unclear
Other bias			
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. - If questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry. - Was there selection bias in the participants chosen? Are they representative and generalisable to the population? - Funders? - Generalisability: Power of the study, were there enough participants recruited to provide strong evidence of a significant difference?	Bias due to problems not covered elsewhere in the table.	Low risk High risk Unclear

Odds Ratio:

The odds ratio (OR) provides an estimate of the relationship between an exposure and outcome.[315] Specifically it provides the associated odds or ratio of an outcome occurring under an exposure (in this instance not being prescribed an antibiotic), compared to the odds of the outcome occurring in the absence of that exposure (in this instance it would be the occurrence of antibiotic therapy).[315, 316] In this thesis the outcome is the occurrence of a more severe infection subsequent to an uncomplicated RTI. The OR calculated for the literature review defines the outcome as the occurrence of a complication (i.e. more severe infection), the exposure includes the absence of an antibiotic treatment, and the OR would assess the probability that a patient with an index uncomplicated RTI exposed to not being prescribed an antibiotic will have a complication compared to the probability of a patient with an index RTI unexposed to not being prescribed an antibiotic i.e. will be prescribed an antibiotic or have delayed antibiotic prescription developing a complication.

A value of one for an odds ratio indicated that the estimated effects are the same in both the exposed and unexposed groups. Where the odds ratio is greater than one, this indicates the associations are greater in the exposed compared to the unexposed groups, and vice versa, where the value of the OR is smaller than one the odds are greater in the unexposed compared to the exposed. Calculations of the OR are often calculated in a 2x2 table as exemplified below.[116, 316]

	Outcome (Complications reported)	**No outcome** (No complications)	**Total**
Exposed (i.e. Not prescribed an antibiotic)	a	b	a + b
Unexposed (i.e. prescribed an antibiotic, or a delayed antibiotic)	c	d	c + d
Total	a + c	b + d	a + b + c + d

Calculation of odds ratio:

$$\text{OR} = \frac{Odds\ of\ outcome\ in\ the\ exposed\ (no\ antibiotics)}{Odds\ of\ the\ outcome\ in\ the\ unexposed\ (antibiotics)} = \frac{a/b}{c/d}$$

Confidence intervals

A confidence interval (CI) is an estimated range of values calculated, for a given set of sample data, which provide with reasonably certainty the range within which the 'true' value lies. The 95% CI is often the range used in research and provides 95% confidence that the true parameter estimate falls within this defined range of values, i.e. the true value lies above the lower value of the CI and below the upper value of the CI. In this way this measure can be used as a representation of the accuracy and precision of an estimate, i.e. estimates with narrower CI would be more reliable than estimates with wider CI, with typically larger studies producing narrower CI than smaller studies. Furthermore, as the CI calculated are for OR (with values which would lie between zero and infinity) if the CI includes the value of one it would be difficult to conclude with certainty that there is a difference in the odds of the outcome in the exposed versus the outcome in the unexposed group.

Calculation of the 95% CI:

$$95\%\ CI = proportion\ \pm 1.96 * standard\ error\ (SE)$$

Standard Error

Standard error (SE) is a measure of the standard deviation of the sampling distribution, otherwise put it's a measure of the statistical accuracy of an estimate providing information on the dispersion of values within the dataset. The following calculation was used to calculate the SE, required for the CI formula.

$$SE = P\sqrt{P * T}$$

Where P is the proportion of outcomes (i.e. proportion of complications) and T is the total number of participants/patients

***P*-values**

The *p*-value is defined as the probability of obtaining the observed estimate, or more extreme, when the null hypothesis (H_0 - This is usually a hypothesis of no association or no difference) is considered true. The use of *p*-values in statistical hypothesis testing is common and often reported alongside odds ratios and confidence intervals. The calculation of a *p*-value involves setting an arbitrary threshold for statistical significance, referred to as α, by convention this is often a *p*-value of 5% (p=0.05). Where the p-value is less than the threshold (p<0.05) this was considered sufficient evidence to reject the null hypothesis of no association i.e. accept that the estimate gives reasonable evidence to support the alternative hypothesis of association. As with any hypothesis test, estimates are prone to a level of uncertainty. The p-value is based on probabilities, hence there is a chance that incorrect conclusions can be made; An α of 0.05 means that there is 95% chance that the null hypothesis is false, and that there is 5% chance that the null hypothesis is true and is incorrectly rejected. Drawing incorrect conclusions are due to type I and type II errors (See table below). A type I error refers to the incorrect rejection of the null hypothesis, this can be reduced by using a lower threshold of α (e.g. 0.001), however this can make detection of a true difference more difficult given the level of precision required. A type II error refers to the incorrect acceptance of the null hypothesis, this is often dependent on the statistical power of a test and can be avoided by using a large enough sample to detect differences.

		Null hypothesis	
		H_0 is true	H_0 is false
Decision	Accept H_0	Correct decision (probability 1-α)	**Type II error** (probability β)
	Reject H_0	**Type I error** (probability α)	Correct decision (probability 1-β)

H0 = null hypothesis

Heterogeneity is an estimated measure of variance between studies. When testing for heterogeneity the null hypothesis would be: all studies are investigating the same outcome effect under the same study conditions. Realistically no two studies will be identical and there will be variation in the study designs, testing methods, participant recruitment, participant eligibility criteria etc. and subsequent study quality. Hence, a systematic review will always have a degree of heterogeneity in the effect measures included by the variant studies. However, it is important to understand the degree and direction to which this heterogeneity between the studies could affect the conclusions made. Vast heterogeneity could render the results difficult to assess and combine in a meta-analysis where the heterogeneity is not accounted for or an attempt at addressing is made.

The degree of inconsistency amongst included studies is often quantified using the I^2 statistic (in conjunction with the *p*-value of the Chi-squared test). I^2 described the total variation across studies which can be attributed to heterogeneity, i.e. not chance alone. The calculation to attain this is as follows (formulae extracted from Centre for Reviews and Dissemination's guidance for undertaking reviews in health care[116]):

Chi-squared test:

$$Q = \sum \frac{1}{SE_i^2}(EE_i - EE_{pooled})^2$$

I^2 statistic:

$$I^2 = \left[\frac{Q - df}{Q}\right] \text{x } 100\%$$

(Where: Q= Cochran's chi-squared statistic as calculated above. df = degrees of freedom

Study	Primary aim	Participant characteristics	Age	Intervention details	Duration of antibiotic treatment	Data collection	Key study observations
Autret-Leca (2002)	To assess the effect of amoxicillin/ clavulanic acid (AMCL) and placebo in the prevention of AOM in children with URTI at high risk of AOM.	Age between 3 months and 3 years with acute upper RTI who are at high risk of AOM (defined as patients with bilateral clear or purulent nasal discharge with cough, fever > 38 C in the preceding 48 h and no AOM; duration of symptoms of URTI present over more than 36 h but less than 5 days; recurrent AOM defined by a history of ≥ two attacks of AOM in the preceding 6 months in children less than 1 year of age or ≥ three AOM during the preceding 12 months in children older than 1 year of age; and with informed parental consent.), treated by private paediatricians during the winter period (Nov-Mar).	Children: 3 months - 3 years	Amoxicillin (100 mg)/clavulanic acid (20 mg) (AMCL) was compared with placebo. Placebo syrup was identical in appearance consistency and taste compared with AMCL syrup. The dose of AMCL was 75 mg kg-1 day-1 (i.e. 25 mg kg-1 every 8 h) for 5 days. Treatment was administered orally. The controls were allowed paracetamol on demand (not exceeding 60 mg kg-1 day-1) and topical decongestants.	The dose of AMCL was 75 mg kg-1 day-1 (i.e. 25 mg kg-1 every 8 h) for 5 days.	• Observation: primary care consultation: All children were re-examined 10 ± 2 days after inclusion. An earlier re-examination was performed whenever parents suspected the development of AOM, or if worsening occurred (e.g. insomnia, anorexia, cough with vomiting, lack of smiling).	• 94 children needed to be exposed to antibiotics to avoid 6 cases of AOM. Intention to treat population: the occurrence of uni- or bilateral AOM at day 10 ± 2 was 16.2% (16/99) in children receiving placebo compared with 9.6% (10/104) in the group receiving AMCL (P = 0.288), a difference of 6.6% (one-sided 95% confidence interval of 14.3%). [Per protocol population: the occurrence of AOM was 16.3% (15/92) and 10.5% (10/95) with placebo and AMCL, respectively (P = 0.251), i.e. a difference of 5.8% (one-sided 95% CI 14.0%).] • No risk factors for development of AOM were found, probably because the population were already selected as at risk (particularly with a history of repeated occurrence of AOM).

Bucher (2003)	To evaluate the effect of a combination product of amoxicillin-potassium clavulanate on adults with acute rhinosinusitis, with a primary outcome of time to cure.	Patients with a history of repeated purulent nasal discharge and maxillary or frontal unilateral or bilateral pain for at least 48 hours but less than 1 month (and presence of pus under rhinoscopy; -only during the first winter season as recruitment was too few).	Adults: 18 years and older	Patients were randomly assigned to receive either amoxicillin, 875mg, and clavulanic acid, 125mg, twice daily for 6 days, or placebo. All patients received decongestant therapy with a xylometazolin hydrochloride spray (Otrivin) and acetaminophen tablets of 500mg (Panadol), with a maximal dose of 3 g/d. Steam inhalation was allowed.	6 days, twice daily.	• Observation: primary care consultation: Physicians recorded a focused medical history for rhinosinusitis-related symptoms, the number of days rhinosinusitis restricted activities at home or work, previous upper RTIs. At day 7 physicians performed a second clinical examination. • Self-reported: Questionnaire on rhinosinusitis-related symptoms and adverse effects from antibiotics was completed at first visit, and day 7 • Telephone follow-up: At days 14 and 28, the study nurse interviewed patients by telephone. • Clinical test: On day 1, collected clinical data on the presence of pus in the pharynx and in the medial meatus during rhinoscopy, pain on pressure and on percussion of the frontal and maxillary sinuses, and body temperature. A radiograph of the maxillary and frontal sinus.	*The median number of days with rhinosinusitis-related symptoms was 5 days in the amoxicillin-clavulanate group and 4 days in the placebo group. *No difference in the time to cure between groups. *At 7 and 14 days, diarrhoea was significantly more likely in the amoxicillin-clavulanate group than in the placebo group. *There was 1 serious adverse event in the placebo group. After 2 weeks of symptomatic treatment, the patient was then treated for 1 week with amoxicillin-clavulanate but experienced a brain abscess. *Unable to show that antibiotic treatment with amoxicillin-clavulanate improves time to cure in adults with clinically diagnosed acute rhinosinusitis. *Adults with a positive rhinoscopy result in antibiotic group had fewer days during which rhinosinusitis restricted their activities at home or work. *Antibiotic treatment offers no benefit for adults with acute rhinosinusitis *Two patients (1.6%) in the amoxicillin-clavulanate group and 5 patients (4.0%) in the placebo group had recurrent rhinosinusitis at 28 day
Chapple (1956)	To evaluate treatment with penicillin or sulphonamide for cases of acute febrile sore throats and the relationship with positive swabs for haemolytic streptococci; predominantly assessing treatment by looking at the duration of illness.	Patients aged more than 2 years seen in general practice, if their doctor thought them to be suffering from an acute infection of the throat or middle ear. Only cases that were of such severity that they would have been given penicillin or sulphonamide were included.	General population: Patients aged >2 years	Three preparations were used: potassium penicillin, sulphadimidine, and a placebo (barium sulphate). They were supplied in powder form by Glaxo Laboratories and were of 3 different sizes to be suitable for different age categories. Bottles were completely filled with water to create suspensions. All nearly identical in appearance and flavour. Doctors were unaware of which suspension the bottles contained. All groups were also given a preparation of a fixed dosage of soluble aspirin tablets in water. (to take twice a day for three days).	4 times a day for 5 days	• Observation: primary care consultation: Each patient was seen twice on follow-up: after 3 days and again at 10-14 days after the start of treatment, with information collected on a medical card. Bottles of medicine were inspected to see whether the solution had been taken correctly. • Clinical test: Nose and throat cotton-wool swabs were taken at the same time as the visits. Urine specimens were also collected on the last visit (10-14 days after treatment).	*The proportion still ill was higher in the placebo group, particularly between 3-5 days from the beginning of trial. *Important to follow-up at day 3 as a proportion of patients required a change to treatment on or after the third day. * 61% of patients in the control group were still ill on the third day, the proportions in the sulphadimidine and penicillin groups were 38% and 31% respectively. * 48 patients included in the trial had red or bulging eardrums at the first visit. Proportion still ill at 3 day follow-up followed a similar trend to sore throat: placebo had the highest proportion (10/16, 63%), sulphadimidine (4/13, 31%), penicillin (6/19, 32%) * Symptoms recurred after apparent recovery in 20 patients; 6 placebo, 11 sulphadimidine, 3 penicillin *10 treatment failures due to acute otitis media: 5 placebo, 4 sulphadimidine, and 1 penicillin. * No cases of rheumatic fever or of persistent discharging ears were found during the follow-up.

Crocker (2012)	To test the hypotheses that children presenting to hospital with community-acquired, radiographic pneumonia or empyema were less likely than community controls to have been prescribed antibiotics at the first GP consultation and to have used antibiotics at any time during the index illness.	Cases were children aged 6 months to 16 years presenting to hospital between October 2008 and December 2009 inclusive, with a working clinical or radiographic diagnosis of pneumonia (including 'consolidation') or empyema. On recruitment of an eligible case, the case's GP and two other practices in close geographic proximity were contacted to identify 6-10 eligible controls from the practice database of children (same age group as corresponding case) who had a recent consultation with a Read code for URTI, LRTI or cough.	Children: 6 months - 16 years	The exposure was antibiotic prescription at the first GP consultation or antibiotic use.	Prior antibiotic treatment or no treatment was measured, no further details stated.	• Self-reported (e.g. diary, questionnaire): Data about index illness, demographics, medical history and potential confounders were collected from carer via self-completed questionnaire. Most probably for this age category completed by the carers rather than cases/controls.	* Antibiotics were prescribed for 31/89 (34.8%) cases and 83/165 (50.3%) controls for the index illness [crude OR 0.53; 95% CI 0.31 - 0.90; P ¼ 0.02]. * Illness duration before consultation was significant effect modifier amongst children consulted 3 days after illness onset, but not among children who waited longer. * There was a longer period of time between first consultation and index hospital presentation among cases who received antibiotics compared with cases who did not {median 5 [interquartile range (IQR) 2.5 - 13.5] days versus median 3 (IQR 2 - 6) days; P ¼ 0.04}. * Two potential confounders: duration of index illness and the date of first GP consultation (before/ during June 2009 versus after June 2009) – cases had a shorter duration of index illness than controls and were less likely to have consulted a GP after June 2009. *Investigated the actual use of antibiotics, important in the context of frequent delayed prescriptions. *Used radiographic definition of pneumonia, not just coding, reducing the potential for misclassification of cases.
Dagnelie (1996)	To assess the effectiveness of symptom resolution of penicillin V compared with a placebo in patients with sore throat who are clinically more suspected of a GABHS infection.	Patients with an acute sore throat with a moderate chance of GABHS; who had three or four of the following clinical features: fever (history); anterior cervical lymphadenopathy; (tonsillar) exudate; and absence of cough. Patients included were aged 4-60 years.	Children & Adults: 4 - 60 years	Either feneticillin (250 mg for 4-9-year-olds, or 500 mg for 10 years and older) or placebo (tablets or capsules, identical in shape and taste), 3 times a day, for 10 days. Paracetamol was provided for 2 days and could be taken when needed (maximum 4 times a day).	3 times a day for 10 days.	• Observation: primary care consultation • Self-reported (e.g. diary, questionnaire): After 2 days: Follow-up examination by GP; registered the degree of sore throat, limitation of activities, absence from school or work, the exudate and anterior cervical lymphadenopathy, and oral temperature. Another throat swab was taken for culturing. *Patients kept a diary registering the degree of sore throat, limitation of daily activities, body temperature and intake of trial medication. *After 14 days, existing complaints were registered by the GP. *Any further complaints were registered with a questionnaire after 6 months.	*After 2 days, fewer of the patients treated with penicillin (36/117; 31%) than of those with placebo (57/117; 49%) still had a sore throat (OR=2. 1; Table 4). This effect only appeared to be present in GABHS-positive patients. A significant difference in the resolution of sore throat was seen (OR=3.8; 95%CI 1.7-8.8) for the GABHS-positive patients (n= 111), but not for the GABHS-negative patients. * 4% (2/56) of the penicillin group compared with 75% (41/55) of the placebo group still harboured GABHS at the first follow-up visit. * 8 placebo-treated patients and 4 penicillin-treated patients were treatment failures. *New episodes of upper respiratory tract infections within 6 months were presented by 15 patients in the placebo group and 14 in the penicillin group. In the 111 patients harbouring GABHS, six out of 55 patients treated with placebo and 10

							out of 56 patients treated with penicillin presented a new episode.
De Meyere (1992)	To explore whether penicillin was superior to placebo in altering the clinical course of proven streptococcal pharyngitis; with the main outcome measure being the difference between Days 1and 3 in sore throat.	Patients aged 5-50 years old, who presented an acute sore throat for less than 5 days. ns. The target population was retrospectively identified by means of the results of a throat culture. Swabs were completed before therapy group allocated and given. Only patients with a positive culture for Group A Beta-haemolytic streptococci were included in the study.	Children & Adults: 5 - 50 years	Phenoxymethylpenicillin (adults 250 mg, and children 125 mg) or placebo were administered, x3 a day for 10 days. Patients (or their relatives) were instructed in the use of aspirin or acetaminophen as needed to control fever and pain. The use of these medications was noted. Topical preparations (gargles, tablets, sprays) were allowed.	10-day duration.	• Observation: primary care consultation: On the first day, baseline symptoms and signs were recorded on a checklist by the physician, with a second evaluation on day 3. • Self-reported (e.g. diary, questionnaire): Patients were asked to complete a diary twice daily for 10 consecutive days. Information was obtained about sore throat, body temperature, malaise, the use of analgesics and whether the patient was able to perform normal daily activities. • Clinical test: measured on days 3 and 20. On Day 3, a urine specimen was obtained in the physician's office for assay for the presence of antimicrobial activity.	*23.2 % of the penicillin group had a sore throat at 3-day follow-up versus 65.9% of the placebo group, difference was 42.7 % (95% CI29.4-56.1%; P<0.0001 Fisher's exact test). *The overall incidence of adverse effects was 14%: 20.8 % in the penicillin group and 5% in the placebo group (P < 0.007). Subjective symptoms, such as itching, dysphagia and nausea, were more frequent in the penicillin group. *No suppurative complications were observed. *Acute symptoms (i.e. sore throat) persisted for an additional day in the placebo group. In the penicillin group on Day 3, 23.2 % of the patients still complained of sore throat versus 65.9 % in the placebo group: difference 42.7% (C.I. 29.4%, 56%). *There was a decrease in the immunological response in the penicillin-treated group. *Results confirm, the acute symptoms and signs of GABHS-pharyngitis are self-limiting.
De Sutter (2002)	To compare the efficacy of amoxicillin vs placebo in patients with an acute upper RTI and purulent rhinorrhoea on the disappearance of symptoms and duration of illness, pain, and purulent rhinorrhoea.	Patients aged 12 years or older, presenting with a respiratory tract infection, and having purulent rhinorrhoea. Purulent rhinorrhoea was chosen as the minimal criterion because it is the symptom most consistently associated with rhinosinusitis in diagnostic studies. and because its presence often leads to physicians prescribing antibiotics.	Older children & Adults & Elderly: 12 years and older	Patients received either: 500mg amoxicillin x3 a day or placebo for 10 days. Patients were allowed to use xylometazoline 1% nose drops and paracetamol or ibuprofen to alleviate symptoms.	10 days amoxicillin	• Observation: primary care consultation: Patients were physically examined by their practitioner. at the start of the study and on day 10. Study ended at day 10 for the patient if they had recovered. Otherwise were follow-ed up again on day 15. • Self-reported: Patients completed an extensive questionnaire to evaluate symptoms at the start of the study and on day 10 follow-up. 20 items of the sinonasal outcome test (SNOT-20) supplemented by 3 questions about pain. Symptoms were scored on a 6-category (0-5) Likert scale. Patients also recorded their daily drug intake (trial medication and symptomatic medication); their general feeling of illness; the presence of nasal discharge, pain, and cough; body temperature; the occurrence of presumed adverse drug effects; and	*Acute URTI with purulent rhinorrhoea do not experience any important benefit from amoxicillin therapy. *Duration of purulent rhinorrhoea was significantly shorter in the amoxicillin group than in the placebo (75% were free of purulent rhinorrhoea after 9 days Vs after 14 days in the placebo group) *7 patients in the placebo (3.4%) withdrew before day 10 because of exacerbation of symptoms versus 1 patient (0.5%) in the amoxicillin (RR 0.25, 95% CI, 0.04-1.56, P = .07). *All 8 patients who withdrew with complaints recovered after starting open antibiotic therapy and had no complications or referrals. *Receiving antibiotics at day 10 follow-up (n = 34: 19 placebo, 15 amoxicillin) or of having to return because of persistent complaints at day 15 (n = 73: 41 placebo, 32 amoxicillin) was not significantly different between the groups (chi-squared test: P = .46 and P = .26). *Diarrhoea was more frequent in the amoxicillin group (29% vs. 19%, RR 1.28, CI 1.05-1.57, P = .02). No difference in incidence of skin rash, abdominal pain, or

						absence from work or school in the first 10 days of study participation.	vomiting. *Absence from work or school was comparable in both treatment groups.
Dunn (2007)	To determine whether giving antibiotics for respiratory infection in general practices provide protection against developing quinsy and attempt to identify individuals at risk.	Patients with an RTI, with no record of a previous RTI within 30 prior to consultation.	General population: GPRD data, not filtered by age	Any record of a prescription for systemic antibiotics (oral or injection) on the day of presentation with RTI or within 30 days of that date was defined as 'positive exposure'.	Database: Type of antibiotic was stratified into penicillin, erythromycin and others.	• Database source (Specify): General Practice Research Datalink (GPRD).	* There were 606 separate quinsy events, but only 192 presented following a recorded, initially uncomplicated sore throat. *Sore throat was most common in the younger age group (<21 years) *Males more likely to get quinsy than females (OR 1.6 CI=1.2 - 2.2), particularly male smokers. *Absolute rate of developing quinsy within 30 days of sore throat is 15.8 per 1000 patient years. Prescription of antibiotics has no effect on the risk of quinsy (adjusted OR= 1.2, 95% CI= 0.7 - 1.8). - There is a suggestion that ABS reduce risk following tonsillitis (OR= 0.6, 95% CI= 0.3-1.3); not significant. * the interval between diagnosis of sore throat and development of quinsy was median of 2 days (IQR= 1-6 days.

Fry (1958)	To assess in a general practice the proportions of patients suffering from readily definable and very common respiratory infections: acute tonsillitis and acute otitis media, who required antibiotics in order to achieve satisfactory results, and the proportions who recovered on non-specific treatment.	Patients who visited general practice with acute otitis media or acute tonsillitis. Acute otitis media was defined as an acute condition with earache and a red drum or with a sudden onset of discharge from the ear, either following earache or arising de novo. Acute tonsillitis/an acute infection of the fauces, was a condition with the sudden onset of a sore throat (young children who do not complain of a sore throat, this is based on diagnosis on other clinical signs) accompanied by redness and swelling of the fauces, with a definite exudate.	General population	An immediate clinical assessment of each patient when first seen, this decided whether antibiotics were necessary. Factors considered: severity of the infection (degree of inflammatory swelling, amount of pain, degree of toxicity and fever); previous history; any peculiarities such as a poor state of general health, whether the standards of home care were poor. Unless there were definite indications for the immediate use of antibiotics these were withheld for the first 24 to 48 hours. If antibiotics were given the drug used was intramuscular penicillin; either a combination of crystalline and procaine penicillins (800,000 units as "abbocillin") or this mixture plus benethamine penicillin (1,250,000 units as "triplopen"). If antibiotics were withheld the patients were seen daily/alternate days, and symptomatic measures (aspirin and gargles) were prescribed.	No set "courses" were used, each case was treated individually with one to four daily injections.	• Observation: primary care consultation: After an immediate clinical assessment was made by the practitioner. The name, age, and sex of the patients were noted, as were the clinical details, the results of bacteriological investigations, the treatment given and the reasons for the choice of treatment, the course of the acute stage, and the state of the patient at a follow-up three months or more from the onset. If antibiotics were not used the patient was examined daily or on alternate days.	*Antibiotics were not provided on the basis of bacteriological results but clinical judgement. The rate with which antibiotics were used was higher (30%) in the streptococcal group than in the non-streptococcal group (19%). *The rates for antibiotics were much higher in adults than in children because of the greater severity of the infection. *The recovery period of tonsillitis were 6 days in the antibiotic group and 5 days in the non-antibiotic group. *The response to penicillin was immediate. In the untreated group the improvement began around 72 hours from onset of tonsillitis/sore throat. *There were no real complications seen in (AOM or) tonsillitis: There were 2 cases of quinsy, which were treated with antibiotics from the outset and cannot be termed complications. No case of rheumatic fever seen. One developed a classical acute nephritis 2 weeks after an acute streptococcal tonsillitis which had been treated with penicillin within 48 hours of onset. *65 patients had recurrence of tonsillitis (majority in adults) and 85 recurrence of AOM (almost all in children under 10 years of age). *Average time for recovery from AOM in those treated without antibiotics was 9 days and in those treated with antibiotics it was 15 days. *Antibiotics were required in 25% of all attacks of acute tonsillitis and 22% of all AOM attacks.

Howe (1997)	Examine the effect of penicillin and cefixime on symptom resolution in a population.	Patients aged 16-60 years, whose presenting complaint was a sore throat, and for whom the GP would normally prescribe an antibiotic.	Adults: 16-60 years	154 patients were eligible for inclusion: 55 were randomised to penicillin (250 mg 4 times a day), 45 to cefixime (cefixime 200 mg daily) and 54 to placebo. Each were prescribed for 5 days. Throughout the trial, patients were allowed to take simple analgesia. The key outcome measure was the change in symptom score between days 1-3.	Each were prescribed for 5 days: penicillin (250 mg 4 times a day), cefixime (cefixime 200 mg daily) and placebo.	• Observation: primary care consultation: questionnaires were completed by GPs also. • Self-reported (e.g. diary, questionnaire): Patients were asked to complete a sociodemographic questionnaire during their initial visit, and to complete a symptom diary daily for 7 days beginning on that day. The symptom diary was based on Likert scales; recording the severity of the sore throat, presence of cough, severity of tender lymph glands, and the extent to which patients felt ill and feverish. • Clinical test: Throat swab was taken at inclusion. At 14 days from presentation, the patient was asked to return to the surgery for a second throat swab.	*Patients with GABHS isolated at recruitment to the study, the proportion of patients who did not have GABHS present after 14 days was 4/10 patients placebo, 8/12 cefixime, and 13/15 penicillin (P=0.055). *Antibiotics can improve rate of resolution of symptoms in patients with a sore throat who are selected for antibiotic treatment by their GP.
Howie (1985)	The influence of antibiotic prescribing for children on the risk of developing rheumatic fever after an acute sore throat.	Children aged 0-13 years discharged from Scottish hospitals with diagnosis of rheumatic fever, with information available from general practitioners about prior sore throat symptoms and antibiotic prescribing.	Children: 0-13 years	Retrospectively assessed whether patients were treated with an antibiotic or not for prodromal sore throat.	Not stated.	• Database source (Specify): Hospital records (using ICD classifications) with additional information obtained from general practitioner records.	The average child has 4 RTIs each year, one of which is presented to a GP. The calculations of risk within the study takes into consideration numbers for patients who would not have consulted a GP (n=9) as part of those patients who were not prescribed antibiotics.

Little (1997)	To assess the medicalising effect of prescribing antibiotics for sore throat; comparing complications and reattendance rates of patients given immediate prescriptions and those managed by other strategies.	Patients aged 4 years and over presented to their general practitioners with sore throat either as principal or subsidiary symptom and showed an abnormal physical sign localising to the throat (inflamed tonsils or pharynx, purulent exudate, faucial or palatal inflammation, cervical adenopathy). For children (under 12 years), who are less likely to complain of sore throat, abnormal signs in the throat were sufficient.	General population: 4 years and over	3 groups: (a) Immediate antibiotic prescribing: a 10 day prescription of phenyoxymethylpenicillin, (b) no antibiotics, and (c) Delayed prescribing: a 10 day prescription of antibiotics to collect if the sore throat had not started to settle after 3 days.	Patients prescribed for 10 days: penicillin V (or erythromycin if sensitive to penicillin), 250mg x4 daily (125mg for 3-5 year olds).	• Observation: primary care consultation: All the notes (from patients and GPs) were reviewed retrospectively in the summer 1996. GPs documentation showed days of illness, physical signs, and antibiotic prescription. At study end GPs were sent a questionnaire asking reasons for non-recruitment other details. • Self-reported: Patients given daily diary to record symptoms and temperature, to be filled until symptom resolution and completed medication. Likert scale was used. • Telephone follow-up: Patients were contacted by research assistants 3 days after first consultation to check no problems filling in the diary. Patients who did not return diaries 2 weeks after entry to the study were telephoned and asked questions addressed by the diary (Retrospective data entry).	*Prescribing antibiotics increased return to the surgery (38% versus 27%), with an additional effect from previous prescribing. A longer duration of illness increased the return rate. *The “delayed” group had the lowest rates of reattendance (hazard ratio of reattendance: delayed 1.00, no antibiotic 1.3 (95% confidence interval 0.86 to 1.97), antibiotic 1.61 (1.09 to 2.38)). *There was no difference between the antibiotic and other groups in the proportion of early returns (respectively 13/238 (5.5%) v 27/437 (6%)) or complications (otitis media, sinusitis, quinsy: 2/236 (0.8%) v 3/434 (0.7%)).
Little (2014a)	To estimate the effectiveness of different strategies of antibiotic prescribing for acute respiratory tract infections on symptom control/severity.	Patients 3 years and over, presenting to a health professional (a GP or nurse) with acute respiratory tract infections (acute cold, influenza, sore throat, otitis media, sinusitis, croup, or lower respiratory tract infection). Patients judged not to need immediate antibiotics were randomised: to four strategies for delayed prescription or no antibiotic prescription.	General population: 3 years and above	889 patients considered for the study. 333 were given immediate antibiotics, the remaining who were judged not to require immediate antibiotics were randomised to: a) no prescription, b) delayed: recontact required for prescription, c) delayed: post-dated prescription, d) delayed: collection of prescription, e) delayed: patient led (that is, the patient was given the prescription). Randomised further into 3 subgroups: i)antipyretic regimens (ibuprofen, paracetamol, or both combined), ii) regular antipyretic versus “as required” dosing, iii)steam inhalation advice versus no advice to inhale with steam.	Not clear what drug/duration/dose were provided; this probably varied by age etc.	• Observation: primary care consultation: Complications were defined as a new consultation documented in the notes within one month with otitis media, sinusitis, pneumonia, quinsy, cervical adenitis, meningitis, or septicaemia. • Self-reported (e.g. diary, questionnaire): Symptom severity and other outcomes were measured using a patient kept 2 week symptom diary. Diary was completed by patients (or children). Using a previously validated format for rating symptoms. • Telephone follow-up: Patients were telephoned (on days 2-3) to check for any problems with diary completion. If no diary was received after 2 weeks, one mailed reminder was sent and then a phone call made as necessary to document key outcomes.	*For the patients who documented taking antibiotics, the median day that antibiotics were started was day 4 for all the delayed prescription strategies and day 1 for the immediate prescription strategy. *In the randomised groups (no prescription and delayed prescription strategies) and the non-randomised (immediate prescription), there was no significant effect of strategy on symptom severity or duration. *Complications were slightly more common in the no prescription group (3/122 (2.5%)) than in the delayed strategy groups (average 6/432 (1.4%)) and similar to the immediate group 8/326 (2.5%). In multivariate analysis controlling for baseline symptoms, smoking, and diagnostic group, there were fewer complications in both the delayed and immediate groups, but this difference was not significant (adjusted risk ratio 0.56 (95% confidence interval 0.13 to 2.37); 0.66 (0.15 to 2.88)).

Little (2014b)	To investigate the likely effect of different antibiotic prescription strategies on complications associated with acute sore throat, and the effect on the non-resolution or progression of symptoms.	GPs in England and Wales were recruited if they reported prescribing immediate antibiotics to 50% or less of patients with tonsillitis, so that the effect of antibiotics could be explored. Eligible patients were previously healthy, aged 16 years and older, with an acute illness (duration 14 days or less), who presented with sore throat as the main symptom, or whose pharynx was abnormal on examination.	Adults: Aged 16 years and older	Antibiotic prescription strategy was recorded in patients: those given no antibiotic, prescribed antibiotics immediately, and prescribed delayed antibiotics. Antibiotic strategy was recorded in 99% (12,677) patients in this cohort study.	Intervention did not compare the effect of one drug but the effect of an antibiotic strategy (i.e. whether prescribed, delayed prescribed, not prescribed).	• Observation: primary care consultation: Clinical proforma: simple one-page clinical proforma (on paper or website) that documented key clinical features to help generate a large prospective cohort. Symptoms were recorded on four-point Likert scales (none, a slight problem, a moderately bad problem, or a severe problem). Clinicians also recorded their prescribing strategy (i.e., immediate antibiotics, delayed antibiotics, or no antibiotics). • Self-reported (e.g. diary, questionnaire): When information about complications was not available from notes, the information was obtained from a freepost card returned directly to the study centre by patients.	*The patients prescribed antibiotics differed significantly from those not given a prescription in several characteristics (particularly fever, pus, and severity of inflammation). * Compared with patients prescribed no antibiotics, the risk of suppurative complications was lower for both immediate antibiotics (RR 0·62, 95% CI 0·43–0·91; estimated number needed to treat [NNT] 193) and delayed antibiotics (RR 0·58, 0·34–0·98; NNT 174). *Re-consultation with new or unresolving symptoms was less common among patients prescribed immediate (RR 0·83, 0·73–0·94; NNT 40) or delayed antibiotics (RR 0·61, 0·50–0·74; NNT 18). *Quinsy and cellulitis are probably prevented by both immediate and delayed antibiotics. Sinusitis most likely prevented by delayed antibiotics and possibly by immediate antibiotics. Benefit of antibiotics for the prevention of otitis media is less clear. *No non-suppurative complications of post streptococcal glomerulonephritis or rheumatic fever were recorded, and many of the complications were minor and self-limiting (e.g., otitis media and rhinosinusitis).

Marchetti (2005)	To evaluate the applicability and effectiveness of practice guidelines based on a wait-and-see strategy for children with AOM. Identify the proportion who at 72 hours recovered from their symptoms (fever and earache) without receiving antibiotics.	Children aged from 1 to 14 years diagnosed with AOM who presented within 24 to 36 hours from onset of symptoms. AOM defined as: the presence of fever (temperature of >38°C rectal or 37.5°C axillar as reported by parents) and/or earache and/or irritability plus 1 or more of the following findings: marked redness, bulging, dullness, and perforation of the tympanic membrane.	Children: 1-14 years old	Antibiotic treatment (amoxicillin, 75-90 mg/kg per day in 3 doses for no fewer than 5 days) was indicated in the presence of otorrhea or a history of recurrent AOM (defined as =>3 attacks in 6 months or =>4 in 12 months). In all other cases, children were given symptomatic treatment only (acetaminophen, 10-15 mg/kg per dose, 4 times a day, and nose washes with a saline solution). 18.8% of cases were treated with either second- or third-generation cephalosporins or macrolides; done so if amoxicillin was previously unsuccessful or the patient had an allergic reaction to penicillin.	No fewer than 5 days amoxicillin treatment.	• Observation: primary care consultation: A follow-up visit 30 days after first contact was arranged • Telephone follow-up: Follow-up was ensured to all cases by a telephone call at 48 to 72 hours after first contact.	*At 30 days, 27 patients had received ABT for a relapse; 42 had received ABT for a new episode of AOM. 716/1099 (65.1%) children recovered without receiving ABT in the non-antibiotic group. * Immediate antibiotics was given to 262 cases, with an additional 272 cases prescribed up until 72 hours later (delayed prescribing total: 534). 743 patients were not prescribed antibiotics up until 72 hours. *There were no complications, including the 1 child who was admitted to hospital owing to concurrent disease (pneumonia). *Believe that it would be difficult to achieve a further reduction in antibiotic use.
McCormick (2005)	Assess the safety, efficacy, acceptability, and costs to parents of immediate antibiotic treatment versus watchful waiting for children with non-severe AOM. Evaluate parent satisfaction with AOM care; resolution of AOM symptoms; AOM failure and recurrence; and nasopharyngeal carriage of Streptococcus pneumoniae strains resistant to antibiotics.	Children with a) symptoms of ear infection, (b) otoscopic evidence of AOM, including middle-ear effusion, and (c) non-severe AOM (as described by severity score in study; based on symptoms and signs).	Children: Children 6 months to 12 years old.	Parents of children received an educational intervention, and their children were randomized to receive immediate antibiotics (amoxicillin plus symptom medication) or watchful waiting (symptom medication only). Immediate-antibiotic group: oral amoxicillin. Watchful waiting group were not given antibiotics. Subjects with AOM failure or recurrence in the immediate antibiotic group received amoxicillin-clavulanate: 90 mg/kg per day. Subjects with AOM failure or recurrence in the watchful waiting received amoxicillin: 90 mg/kg per day. All parents received an electronic thermometer, saline nose drops and/or cerumen-removal drops, ibuprofen and decongestant/antihistamine as needed.	Immediate-antibiotic group: oral amoxicillin, 90 mg/kg per day, 2 doses per day, maximum of 1500 mg/day, for 10 days	• Observation: primary care consultation: Serious AOM-related adverse events were recorded by the research personnel. • Self-reported (e.g. diary, questionnaire): Parents were asked to complete a symptoms diary for 10 days and a satisfaction questionnaire at days 12 and 30.	*No serious AOM-related adverse events were observed. *In the immediate-ABX group, 36% (12 of 33) had AOM failure or recurrence if they had received recent ABX, and 17% (12 of 71) had AOM failure or recurrence if they had not received recent ABX. In the WW group, 52% (14 of 27) had AOM failure or recurrence if they had received recent ABX, whereas 25% (15 of 61) had AOM failure or recurrence if they had not received recent ABX. *Treatment groups did not differ significantly in the number of unanticipated office and emergency department visits, phone calls to the doctor, and days of work/school missed by the parent. *WW seems to be an alternative that is acceptable to parents, reduces the number and cost of antibiotic prescriptions, and reduces the percent of multidrug-resistant bacteria colonizing the nasopharynx of children after an episode of AOM.

Meropol (2013)	Using outpatient ARI visits to estimate the risks of both subsequent serious adverse drug events and community-acquired pneumonia, comparing antibiotic-exposed with unexposed patients.	All primary care visits with Read diagnostic codes (a coding system similar to International Classification of Diseases codes) for acute nonspecific respiratory infections (ARIs) between January 1, 1985, and December 31, 2006, among permanently registered continuously enrolled adults (18 years and older).	Adults & Elderly: 18 years and older.	The exposure of interest was an oral antibiotic prescription within 1 day of the ARI visit, including drugs typically used for RTIs. Excluded drugs used for tuberculosis and for fungal and parasitic infections. Any antibiotic prescription within an illness episode of grouped visits counted as a single exposure. The primary window during which patient considered exposed to antibiotic was within 15 days after the visit, regardless of prescription duration.	Not stated: This may be different for each patient, although national guidelines should be followed by GP.	• Database source (Specify): The UK's The Health Improvement Network (THIN, owned by CSD Medical Research UK), a large primary care electronic medical record database with longitudinal prescription and outcome data. Hospital admissions were identified using the THIN source flags suggested by CSD Medical Research UK to detect overnight hospital admissions. The primary outcome was a severe adverse event within 15 days after the index visit, defined as overnight hospitalization.	*296 hospital admissions for pneumonia within 15 days of the index visit: 180/1,002,050 patients treated with antibiotics, and 116/528,969 patients without antibiotics. *Unadjusted mean incidence rate of pneumonia hospitalisation was 19.33 per 100,000 visits; 21.93 without antibiotic, and 17.96 with treatment; crude risk difference of 3.97 fewer hospital admissions per 100,000 visits for antibiotic-treated patients. *When the window of interest was extended to 30 days, adjusting for the same covariates, the risk difference was 9.35 fewer hospitalizations per 100,000 visits (95% CI, –15.22 to –3.47; P = .002).
Mygind (1981)	Identify whether treatment with penicillin rather than placebo impacts on pain, symptoms of AOM and the acute course of the disease.	Children with AOM (if the child cried with pain, and the tympanic membrane was also red and inflamed) who had had earache for 1-24 hours.	Children: 1-10 years	A granulate of the potassium salt of penicillin-V (Primcillin) was used Vs placebo granulates. With acetylsalicylic acid tablets of 150 mg (only to be taken for earache for at most 3 days, 50mg/kg/day).	Children 1-2 years were given 10ml daily; 3-5 years 20ml, and 6-10 years 30ml for 7 days. Daily dose given as 25% in morning, 25% noon and 50% in the evening (Daily average dose of 55 mg/kg.)	• Observation: primary care consultation: Observation in hospital but not admitted: Follow-up at the hospital after 2-3 days, 7 days, 1 month and 4 months of treatment. Drug intake, completion of the score cards was checked, otoscopy and bacterial culture from the nasopharynx were carried out. Relapses, recurrences and worsening conditions were registered. • Self-reported (e.g. diary, questionnaire): Self-reported survey completed at consultation.	*Significantly less pain in the penicillin group compared to the placebo (P <0.01), until day 3. *symptom scores were more satisfactory in the penicillin group compared to the placebo. *No difference in otoscopy or tympanometry findings between the two groups. *There was no difference between the groups in the relapses between I week and I month (16 and 13%) or recurrences between I and 3 months (27% both). *3 cases of diarrhoea (penicillin 2, and placebo 1) and 1 case with rash (penicillin) *1 child in the penicillin group developed mastoiditis despite repeated periods of antibiotic treatment *During the first week: 1 patient developed pneumonia, and 1 severe tonsillitis. One penicillin-induced exanthema occurred

Petersen (2007)	To determine the extent to which antibiotics reduce the risk of serious complications after common respiratory tract infections.	Patients who consulted with a common RTI: chest infection (excluding those in patients with a diagnosis of pneumonia at baseline), upper RTI, sore throat, and acute otitis media.	General population: General population registered with general practices	Patients who were prescribed an antibiotic on the same day as an RTI consultation, compared to those who were not.	Not stated: This may be different for each patient, although national guidelines should be followed by GP.	• Database source (Specify): The UK General Practice Research Database, with 162 reporting general practices. Follow-up of one month after diagnosis of infection to examine whether the patient had developed a serious complication	*Risk of serious complications in the month after diagnosis was low and was significantly reduced with the use of antibiotics. The number needed to treat to prevent one serious complication was over 4000 for all of these conditions. *Attempted to examine acute rheumatic fever and acute glomerulonephritis as complications of sore throat but found that it was difficult to distinguish between acute and chronic events and there were virtually no cases after sore throat. *Risk of a chest infection in the month after upper RTI was 17 per 1000 in those not treated with antibiotics and 11 per 1000 in those who were treated (adjusted OR 0.64, 95% CI: 0.58 to 0.71, NNT=161). *Risk of pneumonia in the month after a chest infection was high and substantially reduced by antibiotics- varied significantly with age; the greatest protective effect was in those aged 65 and over: Without an antibiotic 4% aged >64 developed pneumonia in the month after a chest infection compared 1.5% with an antibiotic (NNT: 39, between 96-119 in younger ages). *Antibiotics for upper RTI reduced the risk of consultation for chest infection but even without treatment less than 2% of patients consulted with a chest infection in the following month.

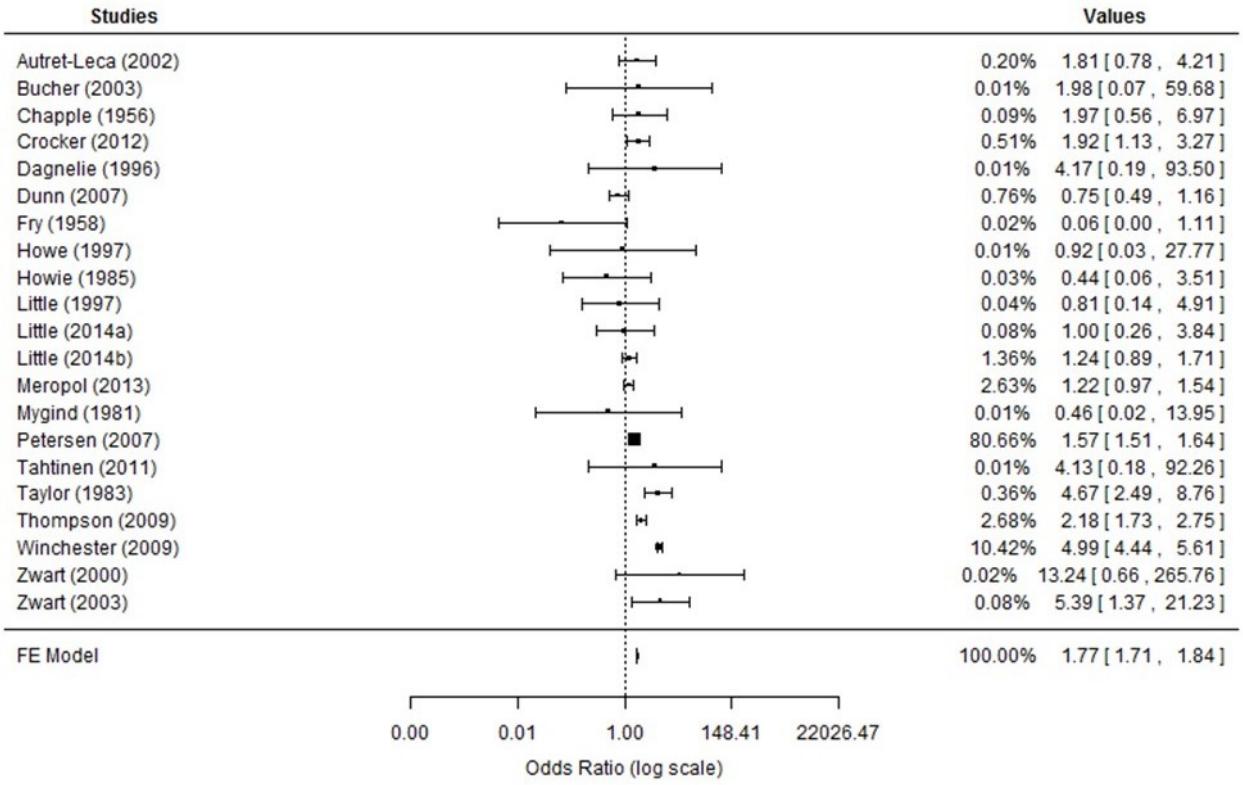
Stalman (1997)	To assess the effectiveness of doxycycline in adults with acute sinusitis-like complaints in general practice; to compare the duration of facial pain and restricted daily activities in each treatment group.	Patients aged 15-65 years who had consulted their GP with symptoms of upper respiratory tract infections for at least 5 days. Inclusion based on diagnostic criteria: 3 main symptoms (complaints after a common cold or influenza; purulent nasal discharge; pain in the maxillary sinuses on bending forward) or two main symptoms and one other symptom (predominantly unilateral maxillary pain, toothache, or pain when chewing.)	Adults: 15-65 years	Patients were assigned to doxycycine or placebo treatment. Doxycycline coated tablets and placebo appeared and tasted the same. Xylomethazoline 0.1% nose drops and steam inhalation for 15 minutes were prescribed in both groups three times a day for as long as the patients had complaints.	10 days: 2 tablets of doxycycline (100mg coated tablets) on day 1 and 1 tablet a day for the 9 following days.	• Observation: primary care consultation: Patients' medical history was recorded by the GP, applying a computerized questionnaire connected to the medical record. After 10 and 42 days, all patients were seen by the GP for evaluation of complaints and a repeat ENT examination. • Self-reported (e.g. diary, questionnaire): The patients recorded the degree of facial pain and limitation of daily activities for 10 days using the McGill-Melzack Pain Questionnaire. • Database source (Specify): Computerized GP questionnaire connected to the medical record. This provided warnings of potential patients to recruit.	*More than 50% of the patients were free of pain at day 4 in the doxycycline group and at day 5 in the placebo group. *Resumption of school or work tended to occur later in patients receiving doxycycline. *Trial medication was discontinued in 12 patients in the doxycycline group and 8 in the placebo group: either that antibiotics were given because of treatment failure (3 and 7 patients respectively) or recurrence (5 and 1 respectively), or that side effects were experienced (4 and 0 respectively). *No complications of sinusitis were reported. *After 10 days 60% of patients were completely cured (according to study criteria)
Tahtinen (2011)	To study the efficacy of antimicrobial treatment with respect to the resolution of symptoms and signs of acute otitis media. The hypothesis was that amoxicillin–clavulanate would reduce the risk of treatment failure.	Children in whom acute otitis media was diagnosed. 3-part criteria required: 1) middle-ear fluid had to be detected by means of pneumatic otoscopic examination that showed at least two of the following tympanic-membrane findings: bulging position, decreased or absent mobility, abnormal colour or opacity not due to scarring, or air–fluid interfaces. 2) at least one of the following acute inflammatory signs in the tympanic membrane: distinct erythematous patches or streaks or increased vascularity over full, bulging, or yellow tympanic membrane. 3) the child had to have acute symptoms, such as fever, ear pain, or respiratory symptoms.	Children: 6 to 35 months	Patients were randomly assigned to receive amoxicillin-clavulanate (40 mg of amoxicillin per kilogram of body weight per day plus 5.7 mg of clavulanate per kilogram per day, divided into two daily doses) or placebo for 7 days. The use of analgesic and antipyretic agents was encouraged, and the use of analgesic ear drops and decongestant nose drops or sprays were also allowed.	Received amoxicillin–clavulanate (161 children) or placebo (158 children) for 7 days.	• Observation: hospital admission/ specialist observation: Day 3 follow-up and an end-of-treatment visit was scheduled for the day after the last dose (i.e. day 8). At this day diaries, used/unused study-drug capsules were returned. Parents contacted study physician whenever they thought that the child's condition was worsened and an additional appointment would be made. • Self-reported (e.g. diary, questionnaire): Parents were given a diary: recorded symptoms, doses of study drugs and any other medications, absenteeism of the child from day care and of the parent from work, and adverse events.	*Treatment failure occurred in 30/161 children (18.6%) who received antibiotics and in 71/158 (44.9%) who received placebo (P<0.001). *Overall, antibiotics reduced the risk of treatment failure by 62% (hazard ratio, 0.38; 95% confidence interval [CI], 0.25 to 0.59; P<0.001) *To avoid treatment failure in 1 child, 3.8 children (95% CI, 2.7 to 6.2) needed to be treated with amoxicillin–clavulanate. *Contralateral AOM developed in 13/159 in the antibiotics group (8.2%) and 29/156 in placebo (18.6%) (P=0.007). *Antibiotics significantly accelerated the resolution of fever, poor appetite, decreased activity, and irritability. No significant effect of on the resolution of ear pain. *AMR was identified from the nasopharyngeal samples of 1 child in the antibiotic group. On days 1 and 8, detected an isolate of Streptococcus pneumoniae that first showed intermediate resistance and later showed full resistance to penicillin. *No cases of mastoiditis. 1 child had pneumococcal bacteraemia, 1 had pneumonia. *Diarrhoea affected 77 children (47.8%) in the amoxicillin–clavulanate group and 42 (26.6%) in the placebo group.

Taylor (1983)	Investigate the risk of a patient developing glomerulonephritis or rheumatic fever after sore throat/inflamed throat illness and whether this risk is influenced by antibiotic prescribing.	Children (0- 13 years)	Children: 0- 13 years	antibiotics prescribed or not, no further details.	Not stated: Database source. This may be different for each patient, although national guidelines should be followed by GP.	• Database source (Specify): ICD codes for outcomes used to recruit patients and further data collected for primary care sore throat and antibiotic use.	Although one region had more cases than expected and one region had fewer, there was no evidence of clinically important clustering by time or geography. - 'Sore throat/inflamed throat' was identified as a prodrome in 39 (49 per cent) of the 79 cases of nephritis - Antibiotics had been prescribed to 18 of these 39 children and had not been prescribed to 21 children, five of whom had consulted their general practitioners and 16 had not.
Thompson (2009)	To determine time trends in mastoiditis incidence, the frequency of antecedent otitis media, and the effect of antibiotics for otitis media on the risk of mastoiditis in children.	All children (3 months to 15 years) who were registered with an "up-to-standard" general practice (indicating that data re-cording by that practice has been verified to meet the required data quality criteria).	Children: 3 months - 15 years	Patients who were prescribed an antibiotic on the same day as an otitis media consultation, compared to those who were not.	Not stated: Database source. This may be different for each patient, although national guidelines should be followed by GP.	• Database source (Specify): The UK General Practice Research Database (GPRD).	*Children treated with antibiotics for AOM, the risk of mastoiditis was 1.8 per 10,000 (139 of 792,623) compared with 3.8 per 10 000 (149 of 389,649) for untreated children (risk difference: 2.0 per 10,000 AOM episodes) *Children had 0.4 (SD:+/- 0.80) episodes of AOM per year, decreasing with increasing age (median age of 5.4 years, IQR: 2.3-7.7). *The incidence of mastoiditis diagnoses was highest in infants, lowest in 2-year-olds, and increased steadily with age thereafter. *The prescription of antibiotics for AOM significantly reduced risk of developing mastoiditis within the following 3 months (OR: 0.56 [95% CI: 0.44 - 0.71]; adjusted for gender, age group, and otitis media diagnosis) *The likelihood of a child receiving an antibiotic for AOM was significantly associated with age (P<.01); older children being less likely to receive a prescription. *4,831 episodes of AOM would need to be treated with antibiotics to prevent 1 child developing mastoiditis *Completely stopping prescribing antibiotics for AOM would result in an additional 2 cases of mastoiditis /10,000 AOM episodes. A total of 255 extra cases of childhood mastoiditis per year in the UK, while reducing antibiotic usage by 738,775 prescriptions per year.

van Buchem (1981)	To evaluate the effect on clinical course (pain, temperature, duration of discharge, otoscopic appearances, audiography, recurrence rate) of four different treatment arms (variations of being given/or not an antibiotic and/or myringotomy) of children with acute otitis media.	Children (2-12 years old) with acute otitis media.	Children: 2-12 years old	Patients were treated with one of the following: 1) neither myringotomy nor antibiotic; 2) myringotomy only; 3) antibiotic only (amoxicillin); 4) both myringotomy and antibiotic. All were given decongestant nose-drops and analgesics (only to be used when in pain).	Amoxicillin ('Clamoxyl', Beecham) 250 mg three times a day for 7 days. The placebo (Beecham) had the same appearance and taste.	• Observation: primary care consultation: Follow-up by the GP was on day 2, 7 and 14. • Observation: hospital admission/ specialist observation: Follow-up by the otolaryngologist after 1 and 2 months and after 1 and 2 years. • Clinical test: tympanic membrane was examined and children aged 4 years or more had an audiogram.	*On the first day earache was rated severe in 131 patients, 24 hours later this had dropped to 20 patients, unrelated to treatment method. *Administration of antibiotics did not have an effect on the number of recurrences during the first 6 months. *During the observation time of c. 2 years there were no cases of mastoiditis or any other complication.
van Buchem (1997)	Effectiveness of antibiotic treatment for primary-care patients suspected of having acute maxillary sinusitis and with an abnormal radiograph. Primary outcome measures for this trial were cure rate and symptoms scores after 2 weeks.	Patients suspected of having acute maxillary sinusitis (acute onset of a common cold with sickness, headache, nose obstruction, discharge, and tapping pain of the maxillary sinus), and for whom antibiotic therapy was considered. Patients maxillary sinus radiograph also had to show mucosal swelling of more than 5 mm, complete shadowing, or a fluid level.	Adults: Adults mentioned but no specific ages provided	Xylometazoline 0.1% steam inhalation (mentholated spirit), paracetamol if necessary, and randomly either with Amoxicillin (a capsule containing 750 mg three times daily for 7 days) or placebo (looking and tasting identical to the Amoxicillin capsules and prescribed in the same frequency for the same duration). After 2 weeks, no further treatment was administered, unless patients visiting the ENT clinic required extra therapy, or a maxillary puncture. The ENT specialist instructed each patient that they experienced recurrent symptoms within a year of follow-up, they should return to their GP, who would examine them and record relapses and complications.	7-day course of antibiotic treatment or placebo.	• Observation: hospital admission/ specialist observation: All participants were seen by an ENT specialist after 1 and 2 weeks; history, physical examination were collected. Notes were made on the number of capsules used and possible side-effects. • Clinical test: After week 2: Erythrocyte sedimentation rate (ESR) and leucocyte count, and a second radiograph of the sinus was made.	*After 2 weeks, 87 (83%) of 105 patients treated with antibiotics versus 78 (77%) of 101 patients treated with placebo had greatly decreased symptoms. *After 14 days, the radiograph on both sides had returned to normal in 74% of the antibiotic-treated patients and in 60% of placebo-treated patients (p=0.03) *Side-effects (mostly gastrointestinal symptoms or rash) were recorded in 28% (definite, and 15% doubtful) of patients given the Amoxicillin and in 9% (definite, and 8% doubtful) of patients given placebo (p<0·001). *In 18 (17%) of the patients treated with placebo and 23 (21%) with antibiotics, a relapse occurred during the follow-up year (p=0.42). *5 patients reported a chronic evolution after 1 year (2 placebo, 3 antibiotics): 2 were found to have an atopic allergy, 2 a hyperreactive rhinitis, and 1 (antibiotic group) was a treatment failure in the trial and found to have polyps in the ethmoid region. *Transition of acute sinusitis to a chronic course has not been observed. No complications occurred during the 1-year follow-up in any other patients.

Winchester (2009)	To investigate the association of antibiotic prescribing and other potential risk factors with hospital admissions and death related to respiratory infections in patients consulting a primary care practitioner for the treatment of an LRTI.	Patients with an LRTI diagnosis during the study period (January 1 to December 31, 2004) were identified in the UK General Practice Research Database (GPRD) using Read codes for acute LRTI (including influenza, pneumonia, and acute bronchitis). The population consisted of patients who, at the beginning of the study period, were enrolled with a primary care practitioner, had been participating in the GPRD for at least 1 year and were at least 1 year of age, to enable the collection of complete morbidity information in the year before the index date (i.e. the first date in 2004 on which the PCP diagnosed an LRTI).	General population: Over 1 year of age	The two outcomes of interest in the 3 months following LRTI diagnosis were respiratory infection-related admission and respiratory infection-related mortality. The effect of exposure to treatment (antibiotic) was investigated.	Not stated: Observational data used, no one antibiotic used or dose. Antibiotics prescribed on the same day as indication was assigned as antibiotic prescribed for that indication (based on coding).	• Database source (Specify): The UK General Practice Research Database (GPRD).	*85.8% of patients with LRTI were prescribed an antibiotic in the community * Rates of LRTI diagnosis were higher in patients 1 to 9 years of age than in those 10 to 19 years of age, increasing steadily with age thereafter. *Over one third (37.7%) of LRTI diagnoses occurred in winter (December, January, and February). *Female patients, patients with asthma or an up-to-date influenza or pneumococcal vaccination had an increased likelihood of being prescribed antibiotics on the index date. Frequent health-care utilization and a number of chronic conditions were associated with a decreased likelihood of prescribed antibiotics *The absolute risk reduction associated with antibiotic prescription on the index date was 0.10%, corresponding to an NTT to prevent 1 RTI-related hospital admission of 1,002 (95% CI, 645 to 3,385). *Antibiotic prescription on index date was associated with significantly reduced risk of hospital admission for 18-64 year olds, but not patients 1-17 years or >64 years *Most RTI-related deaths (1,233;60.0%) took place on the index date *The absolute risk reduction associated with antibiotic prescription on the index date was 0.01%, corresponding to an NTT to prevent 1 RTI-related death of 7,247 (95% CI, 6,757 - 7,937).

Zwart (2000)	To assess whether treatment with penicillin for 3 days and the traditional treatment for 7 days were equally as effective at accelerating resolution of symptoms in patients with sore throat compared with placebo.	Patients aged 15-60 years who contacted their GPs with an acute (seven days or less) sore throat.	Adults: 15-60 years old	Patients were randomly assigned to one of three treatment groups: penicillin V for 7 days, penicillin V for 3 days followed by placebo for 4 days, or placebo for 7 days. The dosage was two 250 mg capsules x3 daily. Paracetamol tablets were supplied to all patients to be used on demand.	Penicillin V for 7 days or penicillin V for 3 days (3 groups assessed, including a placebo group).	• Observation: primary care consultation: 14 days after inclusion the patients were re-examined by their GP, any encounters in the 6 months since initial visit, the GP recorded. • Self-reported (e.g. diary, questionnaire): Patients recorded the extent of throat complaints, the degree of impairment of daily activities, and their oral temperature. They also recorded the number of analgesics used daily and possible adverse effects of penicillin. • Telephone follow-up: After 2, 4 and 6 months the patients were interviewed by telephone on recurrent sore throat and other complaints of the respiratory tract: cough, runny nose, and earache.	*6 patients treated with placebo had a streptococcal complication: 3 peritonsillar abscesses, 1 erysipelas of the hand, 1 impetigo, 1 transient polyarthritis. *Patients had persisting pain, imminent abscess, or a complication in 4 (2%) patients treated for 7 days, 8 (4%) patients treated for 3 days, and 23 (13%) patients treated with placebo. *Patients who took penicillin for 7 days showed resolution of sore throat 1.7 days sooner than those who took placebo. *Patients who took penicillin for 7 days resumed their daily activities 2.0 days earlier than those in the placebo group *Nausea (40%) and abdominal pain (26%) occurred more often in the two penicillin groups than in the placebo group (16% and 15%). *Risk of recurrent sore throat in the 7-day penicillin and placebo groups were similar. *At baseline 442/561(79%) patients had a positive culture result for B haemolytic streptococci
Zwart (2003)	To assess the effectiveness of penicillin for three days and treatment for seven days compared with placebo in resolving symptoms in children with sore throat.	Patients aged 4-15 years who contacted their GPs with an acute (seven days or less) sore throat.	Children: 4-15 years	Of the 262 eligible children 156 were randomly assigned to one of 3 groups: penicillin V for 7 days (n=46), penicillin V for 3 days followed by placebo for 4 days (n=54), or placebo for 7 days (n=56). The dosage was one 250 mg capsule x3 daily for children aged 4-10 and two 250 mg capsules x3 daily for children aged 10 and older.	Penicillin V for 7 days or penicillin V for 3 days (3 groups assessed, including a placebo group).	• Observation: primary care consultation: On the day of and 2 weeks after inclusion the patients were re-examined by their GP and throat swabs were taken, any encounters in the 6 months since initial visit, the GP recorded. • Self-reported (e.g. diary, questionnaire): Parents recorded the children's attendance at school, possible side effects of penicillin, and symptom resolution. • Telephone follow-up: After 2, 4 and 6 months the patients were interviewed by telephone on recurrent sore throat and other complaints of the respiratory tract: cough, runny nose, and earache.	*Mean duration of sore throat was the same in children taking penicillin for 7 days (mean 3.8 days, 95% CI 3.2-4.4) and placebo (3.8 days, 3.3-4.3 *The number of school days missed and incidence of recurrent episodes of sore throat were similar in all groups *Penicillin treatment for 7 days was more effective than treatment with placebo in eradicating group A streptococci (eradication rates were 68% and 28%). *11 children developed a streptococcal sequela: 9 had an imminent quinsy, 1 scarlet fever, 1 impetigo. In the group taking penicillin for 7 days 1 child experienced a streptococcal sequela, 2 in the group taking penicillin for 3 days, and 8 in the placebo group. *The incidence rate ratio of 7 days of penicillin versus placebo was 0.15 (95% confidence interval 0.02 to 1.2) *Possible side effects: abdominal pain (38%), diarrhoea (26%), vomiting (30%) did not differ between the 3 groups. *Increased sore throat recurrence after 1 week, probably due to the 3 days' exposure to penicillin, reducing natural immune response without eradicating the pathogenic streptococci.

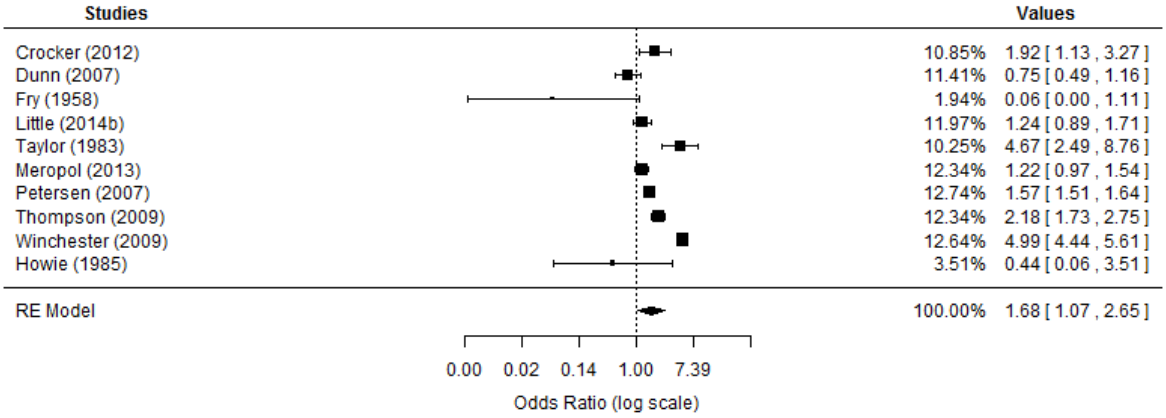


Chi-squared test for heterogeneity (df = 20) = 385.98 (p<0.0001)

I^2 (total heterogeneity/total variability) = 94.82%

Appendix 12. Random-effects meta-analysis results for observational studies and RCTs separately presented (Chapter 2, Page 1 of 1)

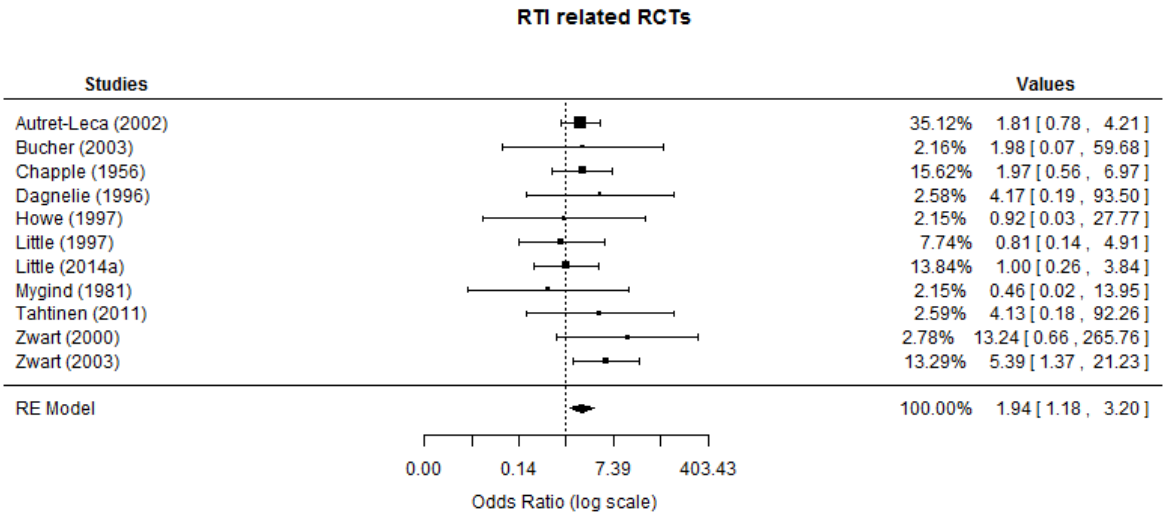
a) Studies of observational design



Chi-squared test for heterogeneity (df = 9) = 378.96 (p<0.0001)

I^2 (total heterogeneity/total variability) = 97.63%

b) Studies of experimental design (RCTs)

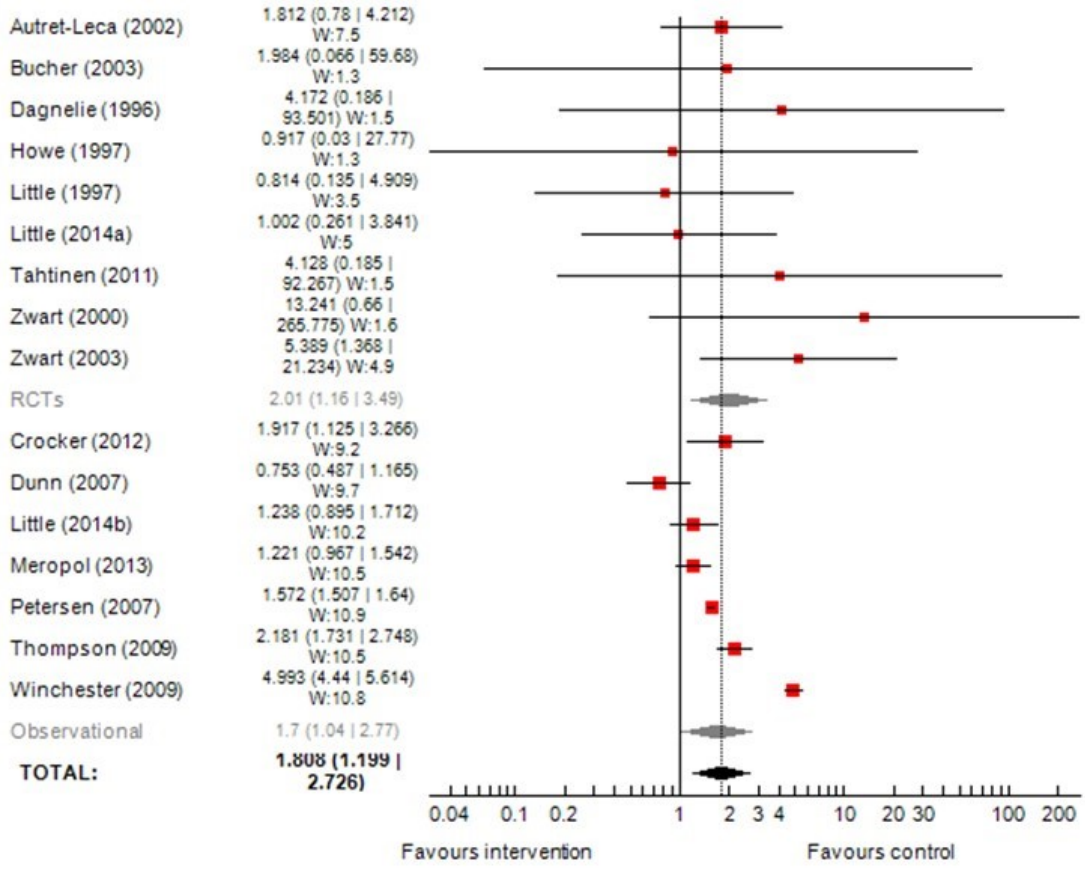


Chi-squared test for heterogeneity (df = 9) = 6.89 (p=0.7361)

I^2 (total heterogeneity/total variability) = 0.00%

Appendix 13. Sensitivity analysis: Random-effects meta-analysis removing studies completed pre-1980s

(Chapter 2, Page 1 of 1)



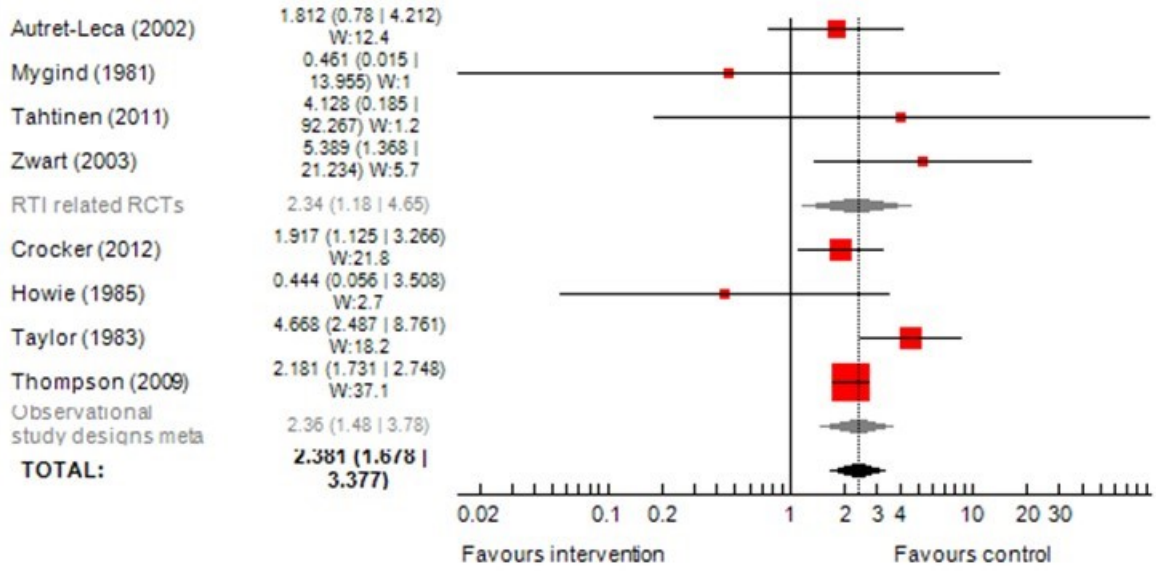
Random effects model overall effect: 1.81 (1.2 - 2.73)

Chi-squared test for heterogeneity (df = 15) = 369 (p<0.0001)

I^2 (total heterogeneity/total variability) = 95.9%.

- Group 1 (RCTs) Q = 6.19 (df = 8)
- Group 2 (Observational) Q = 363 (df = 6)

Appendix 14. Sensitivity analysis: Random-effects meta-analysis studies assessing RTIs in children, by study design (Chapter 2, Page 1 of 1)



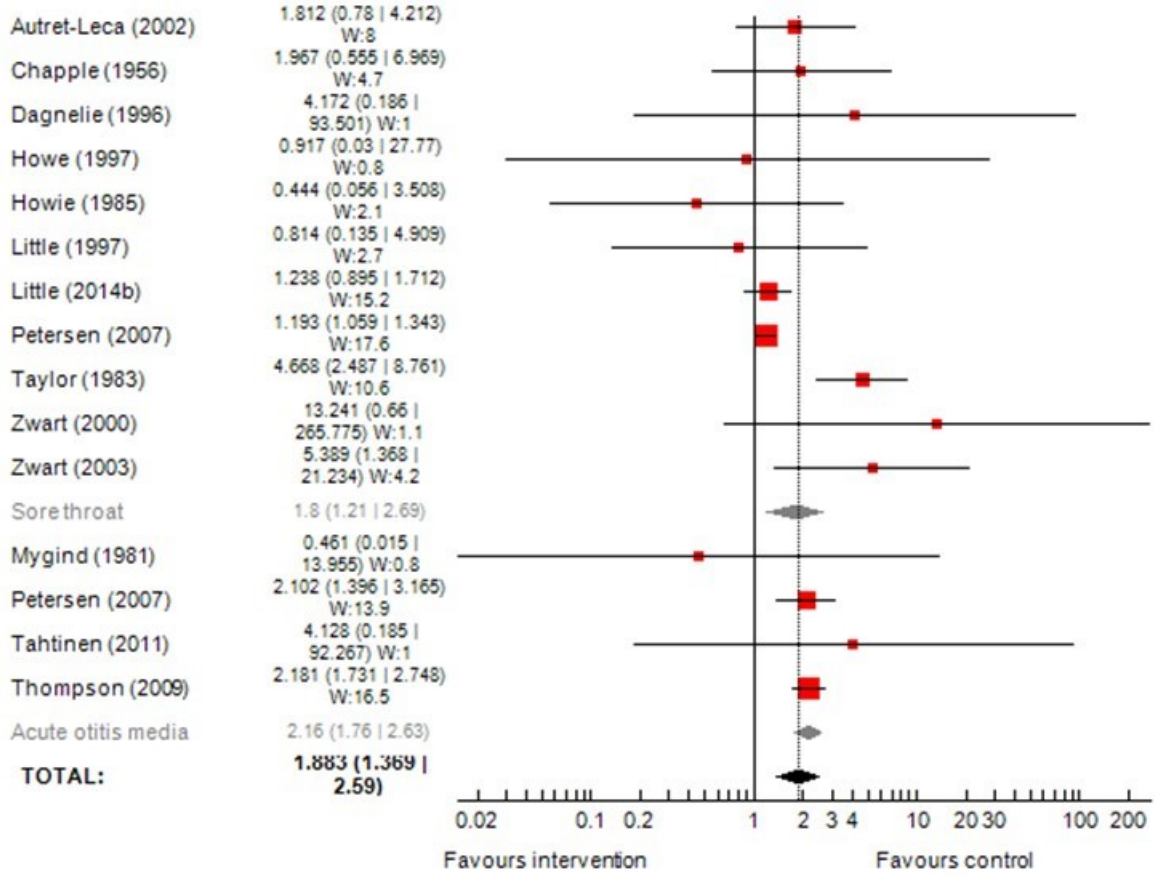
Random effects model overall effect: 2.38 (1.68 – 3.38)

Chi-squared test for heterogeneity (df = 15) = 10.7 (p<0.0001)

I^2 (total heterogeneity/total variability) = 34.6%.

- Group 1 (RCTs) Q = 2.77 (df = 3)
- Group 2 (Observational) Q = 7.93 (df = 3)

Appendix 15. Sensitivity analysis: Random-effects meta-analysis studies assessing specific RTI diagnoses of sore throat and acute otitis media: subgroup and separate meta-analyses (Chapter 2, Page 1 of 2)

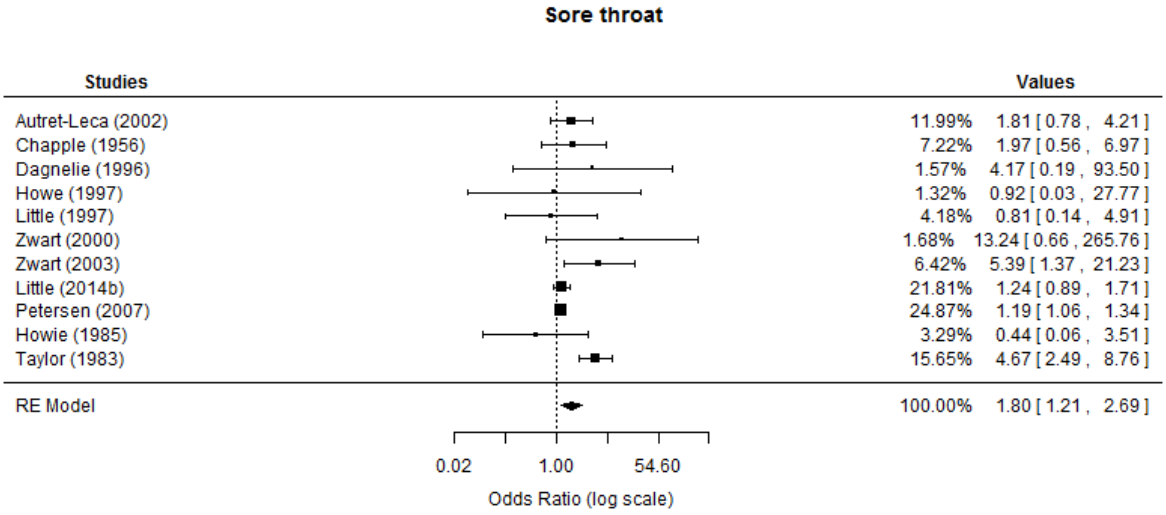


Random effects model overall effect: 1.88 (1.37 – 2.59)

Chi-squared test for heterogeneity (df = 14) = 48.7 (p<0.0001)

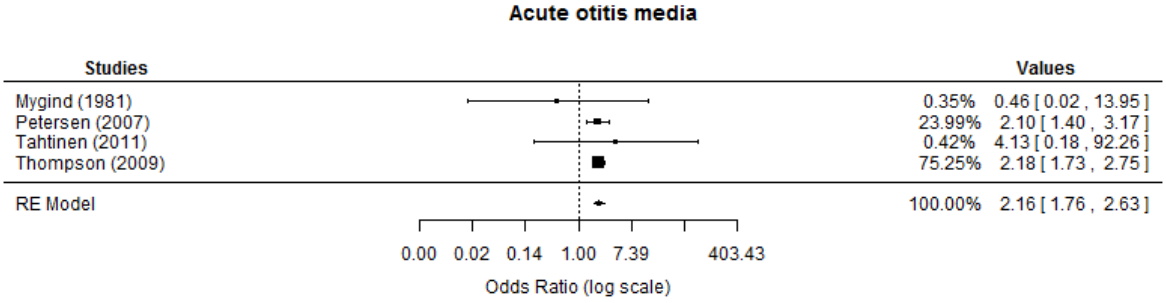
I^2 (total heterogeneity/total variability) = 71.3%.

- Group 1 (Sore throat) Q = 27.1 (df = 10)
- Group 2 (Acute otitis media) Q = 0.978 (df = 3)



Chi-squared test for heterogeneity (df = 10) = 27.096 (p=0.0025)

I^2 (total heterogeneity/total variability) = 63.09%



Chi-squared test for heterogeneity (df = 3) = 0.9784 (p=0.8065)

I^2 (total heterogeneity/total variability) = 0.00%

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL			***by e-mail***
PROTOCOL NO:	16_129R		
PROTOCOL TITLE:	Measuring the potential adverse impact of the adoption of prescribing guidelines in primary care.		
APPLICANT:	Professor Paul Aylin (Professor of Epidemiology and Public Health, Imperial College London, paul.aylin@imperial.ac.uk)		
APPROVED ☐	**APPROVED WITH COMMENTS (resubmission not required)** ☒	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐

INSTRUCTIONS:

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

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

REVIEWER COMMENTS:

The lay summary should be written in plain English for simplicity. Please submit a second version of the research protocol with an updated lay summary for our records. Please note that this should not be regarded as a request for resubmission of protocol.

DATE OF ISAC FEEDBACK:	30/11/2016
DATE OF APPLICANT FEEDBACK:	

For protocols approved from 01 April 2014 onwards, applicants are required to include the ISAC protocol in their journal submission with a statement in the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted.

***** Please refer to the ISAC advice about protocol amendments provided below*****

Amendments to protocols approved by ISAC Version June 2015

During the course of some studies, it may become necessary to deviate from a protocol which has been approved by ISAC. Any deviation to an ISAC approved protocol should be clearly documented by the applicant but not all such amendments need be submitted for ISAC review and approval. The general principles to be applied in regard to the need for submission are as follows:

- Major amendments should be submitted
- Minor amendments need not be submitted (but must still be documented by the applicant and should normally be mentioned at the publication stage)

In cases of uncertainty, the applicant should contact the ISAC secretariat for advice quoting the original reference number and providing a brief explanation of the nature of the amendment(s) and underlying reason(s).

Major Amendments

We consider an amendment as major if it substantially changes the study design or analysis plan of the proposed research. An amendment should be considered major if it involves the following (although this is not necessarily an exhaustive list):

- A change to the primary hypothesis being tested in the research
- A change to the design of the study
- Additional outcomes or exposures unrelated to the main focus of the approved study*
- Non-trivial changes to the analysis strategy
- Not performing a primary outcome analysis
- Omissions from the analysis plan which may impact on important validity issues such as confounding
- Change of Chief Investigator
- Use of additional linkages to other databases
- Any new proposal involving contact with health professionals or patient or change in regard to such matters

* N.B. extensive changes in this respect will require a new protocol rather than an amendment - if in doubt please consult the Secretariat

Minor Amendments

Examples of amendments which can generally be considered minor include the following:

- Change of personnel other than the Chief Investigator (these should be notified to the Secretariat)
- A change to the definition of the study population, providing the change is mentioned and justified in the paper/output [NB previously major]
- Extension of the time period in relation to defining the study population
- Changes to the definitions of outcomes or exposures of interest, providing the change is mentioned and justified in the paper/output [NB previously major]

- Not using linked data which are part of the approved protocol, unless the linked data are considered critical in defining exposures or outcomes (in which case this would be a major amendment)
- Limited additional analysis suggested by unexpected findings, provided these are clearly presented as post-hoc
- Additional methods to further control for confounding or sensitivity analysis provided these are to be reported as secondary to the main findings
- Validation and data quality work provided additional information from GPs is not required

To submit an amendment of protocol to the ISAC, please submit the following documents to the ISAC mailbox (isac@cprd.com)
1. A covering letter providing justification for the request
2. A completed and, if necessary, updated application form with all changes highlighted; if new linkages are required the current version of the ISAC application form must be completed. Otherwise, the original form may be amended as necessary
3. **The updated protocol document containing the heading 'Amendment' at the end of it.** Please include all amendments to the protocol under this heading. No other changes should be made to the already approved document.

ISAC APPLICATION FORM

PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only: Protocol Number Date submitted		**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** ISAC@cprd.com

Section A: The study

1. Study Title

Measuring the potential adverse impact of the adoption of prescribing guidelines in primary care.

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

Yes ☐ No ☒

If Yes, please provide previous protocol numbers:

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

Yes ☐ No ☒

If Yes, please state the name of the reviewing Committee(s) and provide an outline of the review process and outcome:

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

Adverse Drug Reaction/Drug Safety ☐	Drug Utilisation ☐	Disease Epidemiology ☒
Drug Effectiveness ☐	Pharmacoeconomics ☐	Methodological ☐
Health/Public Health Services Research ☐		Post-authorisation Safety ☐

Other* ☐

*Please specify the type of study in the lay summary

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

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

Section B: The Investigators

6. Chief Investigator (full name, job title, organisation name & e-mail address for correspondence- see guidance notes for eligibility)

- Professor Paul Aylin (Professor of Epidemiology and Public Health, Imperial College London, p.aylin@imperial.ac.uk)

CV has been previously submitted to ISAC	☒	**CV number:** 074_16CS
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

7. Affiliation (full address)

Antimicrobial Resistance/Healthcare-associated Infections (AMR/HCAI) Health Protection Research Unit, Faculty of Medicine, Infectious Diseases Department, 8th Floor, Commonwealth building, Hammersmith Hospital, Imperial College London, W12 0HS.

8. Corresponding Applicant

- Miss Sabine Bou-Antoun (PhD Candidate, Imperial College London, s.bou-antoun15@imperial.ac.uk)

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

9. List of all investigators/collaborators (*please list the full names, affiliations and e-mail addresses* of all collaborators, other than the Chief Investigator*)

Other investigator:

- Professor Alan Johnson (Head of the Department of Healthcare-Associated Infections and Antimicrobial Resistance, Centre for Infectious Disease Surveillance and Control, Public Health England, alan.johnson@phe.gov.uk)

CV has been previously submitted to ISAC ☒ **CV number:** 075_16
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator:

- Professor Alison Holmes (Professor of Infectious Diseases and Director of Infection, Prevention and Control at Imperial College Healthcare NHS Trust, alison.holmes@imperial.ac.uk)

CV has been previously submitted to ISAC ☒ **CV number:** 079_16P
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator:

- Dr Ceire Costelloe (Lecturer in medical statistics and Career Development fellow, Imperial College London,ceire.costelloe@imperial.ac.uk)

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

Other investigator:

- Dr. Benedict Hayhoe (NIHR Clinical Lecturer in Primary Care, Imperial College London and a practicing GP, b.hayhoe@imperial.ac.uk)

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

Other investigator:

- Dr. Myriam Gharbi (Research Associate Pharmaco-Epidemiologist, Imperial College London,m.gharbi@imperial.ac.uk)

CV has been previously submitted to ISAC ☒ **CV number:** 073_16S
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator:

- Dr. Violeta Balinskaite (Researcher/Statistician, Imperial College London, v.balinskaite@imperial.ac.uk)

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

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

10. Conflict of interest statement* (please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work)
**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI*

The research was funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London in partnership with Public Health England (PHE). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.
There are no conflicts of interest to declare.

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

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

	Yes	No
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Professor Aylin and members of his team have extensive experience (10+ years) in producing quantitative epidemiological publications related to primary and secondary care outcomes. Dr Costelloe is a lecturer in medical statistics and has substantial experience statistically analysing primary care data.	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Professor Aylin has substantial experience handling CPRD data. (ref: Tsang C, Bottle A, Majeed A, Aylin P. Cancer diagnosed by emergency admission in England: an observational study using the general practice research database, BMC Health Service Research, 2013;13:308-313.	☒	☐
Is experience of practising in UK primary care available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Dr Benedict Hayhoe is a clinical lecturer and researcher in primary care and a practicing GP with experience with the Vision software. He will ensure the research remains firmly grounded in the needs of primary care, with relevance to patients and clinicians.	☒	☐

12. References relating to your study

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

1. NHS England, Quality Premium: 2015/16 guidance for CCGs. 2015. Available from: https://www.england.nhs.uk/wp-content/uploads/2015/04/qual-prem-guid-1516.pdf
2. Public Health England. English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report. PHE. 2015. https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report
3. Petersen I, Johnson A M, Islam A, Duckworth G, Livermore D M, Hayward A C et al. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database BMJ 2007; 335 :982

Section C: Access to the data

13. Financial Sponsor of study

Pharmaceutical Industry	☐ *Please specify:*	Academia	☐ *Please specify:*
Government / NHS	☒ *Please specify:* NIHR	Charity	☐ *Please specify:*
Other	☐ *Please specify:*	None	☐

14. Type of Institution carrying out the analyses

Pharmaceutical Industry	☐ *Please specify:*	Academia	☒ *Please specify:* Imperial College London
Government Department	☐ *Please specify:*	Research Service Provider	☐ *Please specify:*
NHS	☐ *Please specify:*	Other	☐ *Please specify:*

15. Data source

The sponsor has direct access to CPRD GOLD and will extract the relevant data* ☒

A data set will be supplied by CPRD** ☐

CPRD has been commissioned to extract the relevant data and to perform the analyses ☐

Other ☐ *Please specify:*

*If data sources other than CPRD GOLD are required, these will be supplied by CPRD
** Please note that datasets provided by CPRD are limited in size. Applicants should contact CPRD (KC@CPRD.com) if a dataset of >300,000 patients is required.

16. Primary care data (please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies) ☒
EMIS® only* ☐
Both Vision and EMIS®* ☐

Note: Vision and EMIS are different clinical systems, Vision data has traditionally been used for CPRD, EMIS is currently undergoing beta-testing.
**Investigators requiring the use of EMIS data must discuss the study with a member of CPRD staff before submitting an ISAC application*
Please list below the name of the person/s at the CPRD with whom you have discussed your request for EMIS data:

Section D: Data linkage

17. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes* ☒ No ☐

If No, please move to section E.

**Investigators requiring linked data must discuss the study with a member of CPRD staff. It is important to be aware that linked data are not available for all patients in CPRD GOLD, the coverage periods for each data source may differ and charges may be applied. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements before submitting your application.*
Please list below the name of the person/s at the CPRD with whom you have discussed your request:

Helen Strongman (Enquiry Reference: OCR6850)

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

18. Please select the source(s) of linked data being requested:

☒ ONS Mortality Data
☒ Inpatient Hospital Episode Statistics
☐ Outpatient Hospital Episode Statistics
☐ NCDR Cancer Registry Data*
☐ MINAP
☐ Mother Baby Link

☒ Index of Multiple Deprivation
☐ Townsend Score
☐ Other** *Please specify:*

Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. They must also complete a **Cancer Dataset Agreement Form (available from CPRD) and provide a **System level Security Policy** for each organisation involved in the study.*

*** If "Other" is specified, please name an individual in CPRD that this linage has been discussed with.*

19. Total number of linked datasets requested including CPRD GOLD:
3 (ONS Mortality Data, Inpatient HES, [Index of Multiple Deprivation]).

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

Yes* ☐ No ☒

** If yes, please provide further details:*

21. If you have requested linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in response to question 5 above, have access to any of the linked datasets in a patient identifiable form, or associated with a patient index.

Yes* ☒ No ☐

** If yes, please provide further details:*

Professor Aylin has section 251 approval to hold identifiable HES data and analyse them for research purposes (PIAG 2-05(d)/2007). There is a robust system in place to ensure data security. The Dr Foster Unit (DFU) 'Private Network' where all the health data, exists only within the Dr Foster Unit at Imperial Office on the Ground Floor, 3 Dorset Rise, London, EC4Y 8EN. It is a completely independent Local Area Network with no physical connection to the Internet, Imperial College Network or the outside world. The Private Network has no modem, wireless, remote LAN or web access. The Unit's Private Network is an isolated air-gapped network with a mandatory access control system consisting of a number of servers providing data loading, file and database services and statistical analysis. The isolated Local Area Network runs on CAT 5 Ethernet wiring consisting of numerous servers. All data physically resides on disks in the locked air conditioned server room. Only authorised members of the unit have access to this Private Network.

By contrasts the CPRD data for this application will be held on a completely different site, on a different server and access will only be permitted to different named researchers, who have no access to the physical site where identifiable data are held, and where remote access to these data is impossible. There will not be any intention to link the extract separately to identifiable HES data.

22. Does this study involve linking to patient *identifiable* data from other sources?

Yes ☐ No ☒

Section E: Validation/verification

23. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

Yes* ☒ No** ☐

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

24. Does this study require anonymised free text?

Yes* ☐ No ☒

**Please note that work involving free text can only be performed on the July 2013 CPRD GOLD database build or earlier versions. CPRD can provide further advice on the use of anonymised free text.*

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

Yes* ☐ No ☒

* *Please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐
Provision of anonymised records (e.g. hospital discharge summaries) Yes ☐ No ☐
Other (please describe)

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

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

Yes* ☐ No ☒

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

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

Yes* ☐ No ☒

** Please state what will be collected:*

Section F: Signatures

28. Signature from the Chief Investigator

I confirm that the above information is to the best of my knowledge accurate, and I have read and understood the guidance to applicants.

Name: Paul Aylin Date: 08.06.2016 E. signature (type name): P. Aylin

Protocol: Measuring the unintended adverse impact of the adoption of prescribing guidelines in primary care.

A. Lay Summary (Max. 200 words)

The more widely that antibiotics are used, the more likely bacteria are to become resistant to them. NHS general practices (GP) are responsible for the majority of the antibiotics prescribed in the community. There is evidence that prescribing antibiotics is not always necessary, for some conditions a patients' recovery time with or without antibiotics is similar and therefore antibiotic prescribing is often inappropriate.
To counteract the increase in resistance to antibiotics seen, new antibiotic prescribing targets have been published to encourage general practices to reduce antibiotic prescribing.

Where a treatment is required for a bacterial infection and the treatment time is delayed, or where treatment is not provided, a more severe infection may develop as a consequence. A more serious infection, including infections of the blood, would increase a patient's risk of severe illness and death.

The purpose of this study is to use routinely collected data from a sample of GPs and hospitals across England, to investigate the effect of a national intervention (introduced to reduce antibiotic prescribing) on levels of primary care prescribing and the associated unintended health outcomes that may occur consequently. Findings from this study would contribute to wider evaluation of the quality premium/policy change.

B. Technical Summary (Max. 200 words)

Antibiotics differ to other medical drugs, as their overuse and misuse selects resistance and weakens their effectiveness. The threat of antimicrobial resistance has been of growing public health concern, with the apprehension that many common and serious infections will become increasingly difficult to treat, if not entirely untreatable with pan-resistant infections.
In response to the increase of antimicrobial resistance, quality premiums were introduced to improve antibiotic prescribing. This change should impact and reduce unnecessary antibiotic exposure, with the intention of easing or slowing the rate of resistance.
A reduction in overall antimicrobial prescribing however, may be accompanied with a reduction in appropriate therapy. A delay in treatment where antibiotics are required permits bacteria to propagate and may cause more severe infections or other clinical complications, e.g. bacteraemia, death.
This study will analyse linked Clinical Practice Research Database (CPRD), Hospital Episode Statistic (HES) and Office for National Statistics (ONS) data to examine a patient's pathway through the healthcare system and distinguish any adverse outcomes related to the introduction of the quality premiums. Time series analysis will be completed to examine changes in the time trends of prescribing antibiotics and adverse outcomes, prior to and following the intervention (i.e. the Quality premium).

C. Objectives, Specific Aims and Rationale

Following the implementation of the quality premiums to reduce antimicrobial prescribing in the primary care setting, the objectives of the study are to determine whether there has been a reduction in prescribing of antibiotics and whether there are any subsequent unintended adverse outcomes.

The specific aims include:

1) To analyse whether there has been a reduction in prescribing in primary care for respiratory tract infections (RTI), urinary tract infections (UTIs) and skin and soft tissue infections (SSTIs) pre- and post-intervention (i.e. introduction of 2015/16 quality premiums).
2) Using routinely collected data to look at the possible adverse impact of reducing antimicrobial prescribing at a national level. Specifically to examine whether there has been a subsequent effect on:
   - The occurrence of disease (i.e. subsequent more severe infections)
   - An increase in the severity, as indicated by hospitalisation or death

Rationale:
There is currently limited research into the likely clinical effects of reducing use of antibiotics in primary care on patient safety and no research which quantifies the impact nationally. These specific aims will permit us to examine whether the introduction of 2015/16 quality premiums, designed to reduce antimicrobial use in the community, has had a subsequent attributable impact on patients safety and outcomes i.e. sickness/death.

D. Background

The use of antimicrobial drugs globally and in England is widespread and the subsequent presence of bacteria resistant to these antimicrobials is increasing. The threat of antimicrobial resistance and the requirement for appropriate use of antibiotics was highlighted in the 1998 World Health Assembly.(1) Since then, the Chief Medical Officer's annual report published in 2013 called for a healthcare-system-wide action towards preserving antimicrobials,(2) this spurred the publication of the UK Five Year Antimicrobial Resistance Strategy 2014-18. The five year strategy describes three strategic aims, one of which includes the requirement to "conserve and steward the effectiveness of existing treatments", with one of the emphasis being on improvements to the quality of prescribing in primary and secondary healthcare settings.(3)

Quality measures for primary and secondary care were published in 2014, for primary care the measure reflected a reduction in total antibiotic and broad-spectrum antibiotic consumption.(4) Quality premiums were put into effect in 2015 based on these national and local priorities. These quality premium incentives were intended to reward Clinical Commissioning Groups (CCGs) for improvements made to the quality of health services commissioned by that CCG and for the associated amelioration in health outcomes. The 2015/16 Quality Premium guidelines reflect a measure to improve antibiotic prescribing in primary and secondary care, which equates to 10% of the quality premium. This composite indicator is made of three parts, two of which refer to primary care prescribing: Part A refers to a reduction in overall antibiotic prescribing for each CCG of 1%, or more, from the 2013/14 values; Part B focuses on a reduction in broad-spectrum antibiotics prescribing (co-amoxiclav, cephalosporins and quinolones), with a required decrease in proportion for each CCG of 10%, or below the 2013/14 England median proportion for 2013/14.(5)

This drive to reduce primary care prescribing is in response to prevailing increases seen in prescribing in the community setting. The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report detailed a 6% increase in the total use of antibiotics from 2010 to 2013.(6) The report also identified that the majority of prescribing in England occurs predominantly in general practices (78.5% in 2013).(6)

Research states that various diagnoses which present to GP practices may be prescribed antibiotics where not necessarily needed; Circa 90% of sore throat and 80% of acute sinusitis cases are thought to resolve without antibiotics.(7) Acute respiratory tract infections (RTIs), urinary tract infections (UTIs) and skin and soft tissue infections (SSTIs) are the most common reasons for patients to consult with their GPs and are also the most common indications for empirical antibiotic prescribing in primary care.(8, 9) This study will for this reason focus on consultations for patients with diagnoses related to these infections.

With a reduction in antibiotic prescribing there is concern around patient safety. A reduction in antibiotic prescribing aimed to decrease resistance rates, may be accompanied with a reduction in appropriate therapy. A delay in treatment where antibiotics are required may permit more severe infections to occur or other clinical complications, as an adverse consequence of prescribing reduction.

E. Study Type

This will be an observational hypothesis testing study. The hypothesis is that subsequent to the introduction of the quality premiums, there are reductions in antimicrobial prescribing in the primary care setting causing adverse unintended consequences (more severe infections/ secondary infections/ hospital admission/ mortality). A population-based retrospective study will be conducted. The study is retrospective because both the exposure data (sourced from the CPRD consultation and prescription data) and the outcome data (sourced from HES, ONS and the CPRD consultation data) are already available either within or linked to the CPRD database.
The study period will be April 1st, 2010 – March 31st, 2017 (-/+ 60 days). A 6 year study period provides a period long enough to analyse any time trends, by month adjusting for seasonality. We can establish baseline analysis of GP consultation, prescription and outcome trends prior to the 2015/16 Quality premiums as well as post-intervention.
To attain an answer to the hypothesis and aims, the study will be broken into four studies (1, 2a, b, c), focusing on three common infections (RTIs, UTIs, SSTIs), explained below.

Definition of 'complication' or 'unintended consequence':
Cases will be patients who have developed a severe infection (e.g. community acquired pneumonia, pyelonephritis, mastoiditis, quinsy, rheumatic fever, scarlet fever, bacteraemia/sepsis; list is in Appendix) subsequent to the READ code diagnosis of RTI, UTI, SST. The episode duration will vary for the different study outcomes; i.e. 60 day period for bacteraemia, whereas 28 days for rheumatic fever.

F. Study Design

1. A ***descriptive study*** investigating the reduction in antibiotic prescribing: Population-based retrospective descriptive, time series analysis (TSA; ARIMA model) will be used to identify the trend in Antibiotic prescriptions in patients who consulted for RTIs, UTIs, SSTIs. An interrupted time series (ITS; ARIMA model) analysis will be completed to identify the impact of the quality premium on antibiotic prescribing.
2. A ***descriptive study*** investigating associated unintended consequences:
    a. A descriptive study and correlation of a count over time of complications following initially consultations with RTI, UTI and SSTIs. TSA (ARIMA model) study will be completed to identify the trends in complications for patients who initially consulted for RTIs, UTIs, SSTIs. An ITS (ARIMA model) will be utilised to identify

the impact of the QP on complications. Cross correlation to find whether there is an association between QP impact on antibiotic prescribing and complications.

b. A descriptive study, time series analysis (TSA; ARIMA model) will be used to identify the trend in unintended consequences, unrelated to primary consultation i.e. complications for all patients. This sub-analysis will look at overall counts of the outcomes, unrelated to initial GP visit.

3. ***Retrospective cohort study,*** comparing patients presenting with RTI, UTI, SSTI pre- and post-QP, who did or did not receive an antibiotic prescription. This study design has been included in order to take into account patient risk factors i.e. we can adjust for variations between individuals (e.g. age, sex, ethnicity) and GP practice level (e.g. deprivation, region).

G. Sample Size

Time series and interrupted time series analyses relies on there being a minimum of three time points pre- and post-intervention, which the study design and duration has taken into account.

The study is mainly descriptive in nature and therefore has not been powered to detect specific changes in rate of complicated infection. As the unintended consequence outcomes of interest in this study are at times rare, outcomes will be aggregated to produce a binary variable ('complication experienced': Yes/No) related to RTI, UTI or SSTI. Based on previous literature and using exemplar for complications associated with each of the diagnosis of interest the below samples would be required to detect clinically meaningful changes in complication rates.

- RTI sample size:
  The literature suggests that 1.4% (0.0137) of patients develop complications (quinsy, sinusitis, otitis media, cellulitis or impetigo) (Little et al., Lancet Infect Dis, 2014). To detect a clinically significant increase of 10% in complications (0.0151) following a decrease in antibiotic prescribing, a total of 286,696 patients (143,348 per group) would be required (2 sided α=0.025 (Bonferroni correction), β=0.80).
- UTI sample size:
  The literature suggests that 1.3% (0.013) of patients with a UTI develop pyelonephritis (Christiaens et al. BJGP, 2002). To detect a clinically significant increase of 10% in complications (0.0143) following a decrease in antibiotic prescribing, a total of 303,200 patients (151,600 per group) would be required (2 sided α=0.025 (Bonferroni correction), β=0.80).
  Preliminary analysis based on CPRD suggests approximate yearly average of 200,000 UTI clinical events, (using appendix Medcodes). Hence, the sample would be large enough to detect an increase in complications, and we are utilising more than 1 year of data.
- SSTI sample size:
  Despite interest in antibiotic prescribing and SSTI related complications there have been very few published papers on this. The literature suggests that up to 5% (0.05) of patients with impetigo develop acute poststreptococcal glomerulonephritis (Cole et al. AFP, 2007). To detect a clinically significant increase of 10% in complications (0.055) following a decrease in antibiotic prescribing, a total of 75,648 patients (37,824 per group) would be required (2 sided α=0.025 (Bonferroni correction), β=0.80).

H. Data Linkage Required (if applicable)

This study will require CPRD data to be linked with HES and ONS data. The CPRD data will be required for the patient demographic details, diagnostic and prescribing data for initial and subsequent visits to GPs, as well as for outcomes seen in primary care.

The HES data will inform on the clinical outcome of any admissions into hospital. ONS data will provide mortality information, reason for death and whether the patient was lost to follow-up; unrelated to infection. The Index of Multiple Deprivation (IMD) data will be used as a proxy for socio-economic status, and required to improve regression analysis.
Where a patient has not been able to be linked across the datasets, we will not exclude these patients as the initial analysis will be based on CPRD prescription records linked to CPRD consultation records. We will only restrict the study population to patients with records in the CPRD-HES linked dataset when looking at the secondary care outcomes for patients admitted during the HES coverage period. Restricted to CPRD-ONS mortality dataset when investigating related mortality during the ONS mortality coverage period. Patients who are eligible for HES linkage but not for IMD will not be excluded and similarly for ONS linked data. Linkage to ONS and HES will occur for the data available and replicated if possible for when the coverage period of the linkage data matches the duration required (set 12 currently extends to 31/10/2015). Patients will be included in the study from April 1st, 2011 – March 31st, 2017 (data required for -/+ 60 days).
Professor Aylin also works within another research unit with researchers who have access to patient-identifiable HES data, however Professor Aylin himself does not have access to this patient identifiable data. The data is held on a completely independent Local Area Network and staff members working on this network have to be physically present at their desks in the organisation's Research Office. The private network can only be accessed by direct connection. VPN's (Virtual Private Networks), Extranets, wireless networks and Remote Access are NOT allowed. The researcher on our team has no access to these data, and only named researchers working under him at another research unit have access to the identifiable data. By contrast, the CPRD data for this application will be held at a completely different site, on a different server and access will only be permitted to different named researchers, who have no access to the physical site where identifiable data are held, and where remote access to these data is impossible.

I. Study Population

For sub-analyses 1, 2a, 3 the same extract and study population will be used: The study population will be all patients with a permanent registration status in up-to-standard English GP practices (indicating that data recorded by that practice has been verified and meets required data quality criteria), diagnosed with primary infections commonly seen and prescribed antibiotics in primary care (i.e. RTI [including Ear, Nose and Throat infections], UTI, SSTI; list available in Appendix), within the study period of April 1st, 2010 – March 31st, 2017 (-/+ 60 days).
Data will be aggregated by month for TSAs and ITS. Recruitment of patients will occur throughout the study period, with follow-up to distinguish whether the patient developed a complication due to a lack of antibiotics. An episode will be defined as a newly recorded single consultation that is not preceded by a consultation for the same or similar diagnosis, reported within an episode duration. A prescription will be linked to a patient's consultation if both occurred on the same date.

Sub-analysis 2b will require a smaller extract as the majority of outcomes are rare; The study population will be all patients with a permanent registration status in up-to-standard English GP practices diagnosed with the outcomes of interest (list available in Appendix), unrelated to any previous consultation, between April 1st, 2010 – March 31st, 2017 (-/+ 60 days).

Inclusion criteria:

- The study population will include all CPRD "acceptable" (at the time of recruitment and during follow-up) patients with a permanent registration status and who have not 'opted out' from providing data in up-to-standard participating English GP practices.
- 1, 2a, 3) Patients with a primary visit at a GP practice related to diagnoses of interest who have not been prescribed an antibiotic 30 days prior to primary visit.
    - 2a) Where the outcome of interest in the TSA is unintended consequences as measured by admissions into hospital, patient eligible will be the same as that stated above, as well as those patients who have valid identifiers (NHS number, postcode) for linkage with HES data, have not opted out of the linkage scheme, and have been admitted to hospital during the HES coverage period (to the 31/10/2015 in set 12, due for release end of March 2016).
    - 2a) Where the outcome of interest in the TSA is unintended consequences as measured by mortality as an unintended consequence, patient eligibility is as above, however for patients who have died during the ONS coverage period (to the 31/10/2015 in set 12, due for release end of March 2016).

Exclusion criteria:

- Patients who are temporarily registered with a GP will be excluded to avoid duplication of data, as these patients will most likely be permanently registered elsewhere.
- 1, 2a, 3) Excluding prevalent cases: Patients who had a diagnosis before the study index date, or have been prescribed an antibiotic 30 days prior to the study start date. Patients with multiple records for diagnoses (e.g. sore throat, quinsy) will be counted as separate episodes only if the diagnoses dates (for the same diagnosis) were at within episode duration. Duplicate (e.g. within 30 days of index date) episode of infections will be removed during the majority of the analysis, however will be required to distinguish the number of revisits to GP practices for the same diagnosis.

J. Selection of comparison group(s) or controls

1, 2a, 2b) As a time series analysis and interrupted time series will be utilised, a comparison/control is not required as the pre-intervention arm acts as the control (matching by practice). Any differences in adverse consequences between these two groups can be used to evaluate direct effects of the reduction in prescribing; both the exposed (post-policy) and unexposed (pre-policy) groups have attended a GP practice for similar diagnoses, it is only their treatment which will differ.

3, Cohort study: The unexposed/control group will be those patients who attend GP practices for RTI, UTI, SSTI related diagnoses prior to the implementation of the QP (April 2015). Matching these to the exposed; patients from the same GP post-QP (i.e. controls are identical with the exception of exposure).

K. Exposures, Outcomes and Covariates

Exposures:
1) ITS analysis: The introduction of the quality premium in 2015/16.
2 a, b) ITS analysis: The introduction of the quality premium in 2015/16 (and the expected decrease in prescribing following the intervention).
3) The exposure will be whether a patient's initial consultation was post-QP i.e. post April 2015.

Outcomes of interest:

1) **Antibiotic prescription** rate: Have prescribing practices of antibiotics altered? Has there been a reduction in antibiotic prescribing since the introduction of the quality premiums; assessed by identifying variations in:
   - Proportion of patients prescribed antibiotics for diagnoses of interest
   - The number of antibiotic items per STAR-PU (specific therapeutic group age-sex weightings related prescribing units).
   - Stratifying measures above by total or broad-spectrum antibiotics (co-amoxiclav, cephalosporins, quinolones).
2) **Incidence of adverse consequences**. Primary and secondary care outcomes have been identified in the Appendix (CPRD and ICD-10 codes). A summary table is provided below of the codes included.
   a) Incidence in primary care as well as an increase in severity will be assessed; as indicated by hospital admission (for the same or clinically related condition during 60 days following diagnosis) and mortality (60 day-all cause mortality from initial consultation).
   b) Count of unintended consequences by month (unrelated to primary consultation)
3) **Cohort:** Odds ratio between exposed (post-QP) and unexposed (pre-QP) group, for RTI, UTI and SSTI.

Summary table of the outcomes of interest and the CPRD and ICD10 codes which have been included in the appendix:

RTI related	**Otitis media related**
Pnuemonia (CAP)	Mastoiditis
Quinsy/ peritonsillar abscess	Meningitis
Rheumatic fever	Brain abscesses
Scarlet fever/ scarlatina/ strep throat	
Empyema/ pyothorax/ purulent pleuritis	
complicated UTI	**Complicated SSTI**
pylonephritis	Fasciitis
Pyelitis	Necrosis
Renal/perinephric abscess	Cutaneous abscesses
Infection of kidney	Boils
Prostatitis	Folliculitis
Prostatocystitis	(strep throat)
Complicated intra-abdominal infections	**Other**
peritonitis	Sepsis/ Septicaemia/ BSI/ bacteraemia

Covariates:

Specific conditions will have different comorbidities/covariates included in regression analyses. The below however is a more comprehensive list:

- Demographic: Age; sex; deprivation gradient/SES; smoking; alcohol; BMI.
- Underlying diseases/comorbidities: diabetes; dementia; cardiovascular (i.e. stroke/cerebrovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease); liver disease; renal disease; ulcer disease; respiratory diseases (i.e. COPD, asthma, allergic rhinitis); craniofacial or neurological abnormalities; STIs;

immunocompromised/ have an autoimmune disease (any tumour, leukaemia, lymphoma, metastatic solid tumour, HIV positive or AIDS).

- Other: Number of routine medications (other than antibiotics, e.g. inhaled corticosteroids); taking drugs that interact with antibiotic availability (oral contraceptives, coils etc.); antibiotic allergies (especially to penicillin); pregnancy status; type of immunisation/vaccination (i.e. pnuemoccocal and influenza vaccination status [immstype, stage and status]); length between GP diagnosis and hospital admission; season (split using months).

L. Data/ Statistical analysis

The analysis plan will include:

1) Antibiotic prescribing study:
   - Descriptive study: count and proportion over time of antibiotic prescribing (total antibiotics and by 3 broad-spectrum antibiotic groups [co-amoxiclav, cephalosporins and quinolones]) for patients consulting for RTI, UTI, SSTI.
   - The number of antibiotic items per STAR-PU (specific therapeutic group age-sex weightings related prescribing units) by diagnosis group and by total and broad-spectrum antibiotic prescribing. STAR-PU are weighted units which will allow for comparisons which have been adjusted for age and sex of patients at the practice level.
   - The above STAR-PU trends will be imputed into a Time Series Analysis (TSA). TSA is a robust quasi-experimental method used to examine longitudinal trends. An ARIMA model will be used. The TSA trend analysis will be followed by an Interrupted Time Series analysis (ITS) which examines the effects and changes in time trends following an intervention i.e. the introduction of the quality premiums. An ARIMA sequential segmented linear regression model will be used to analyse the decrease in antibiotic prescribing by diagnosis group. Data will be aggregated by month over a 7 year period, pre- and post-policy implementation (with 2 years/24 month time points of post-policy data; 60 months pre-intervention). Stratifying by: Antibiotics group (Broad-spectrum/Total), diagnoses group (RTIs, UTIs, SSTIs), age groups (particularly as the infections affecting the very young and old may vary significantly).
2) Unintended consequences:
   a) The occurrence of unintended consequence:
   - Descriptive study: count and proportion over time of unintended consequences for patients consulting for RTI, UTI, SSTI; identifying whether there are any significant trends seen in children Vs adults.
   - TSA, ARIMA model, to analyse trend in unintended consequences (outcomes seen in primary care, hospital admissions and related mortality) and the correlation between the unintended consequences and prescribing (obtained from sub-study 1).
   - ITS, ARIMA model, sequential segmented linear regression model will be used to analyse the change in levels of both antibiotic prescribing by diagnosis group (completed in sun-study 1) and the occurrence of the unintended consequence doing so by using cross-correlation analysis (Pearson test).

   b) The occurrence of unintended consequence, irrespective of previous consultations
   - Descriptive count of outcomes of interest over time, by month, imputed into a TSA and ITS, ARIMA models.

3) Cohort study:
   - Comparison of unintended consequences between patients who had presented with RTIs, UTIs, SSTIs before the implementation of the QP (unexposed) to those who presented post-QP (exposed) (Odds ratio).

- Hierarchical multivariate logistic regression will be used to assess whether exposed patients are at an increased risk of an unintended consequence; i.e. examine association between 'exposure' to the QP and outcome of 'experience of a complication'.
    - The multivariate model will be adjusted for antibiotic exposure and variations at the individual- (e.g. age, sex, comorbidities). A second, hierarchical model will adjust for clustering at the GP practice (e.g. prescription rates, consultation rates, size of the practice, deprivation, region), and will provide a combined influence on the outcome. Logistic regression will be used as the outcome is binary, a median Odds Ratio (mOR) will be calculated.

Statistical analysis will be performed using Stata12 (STATA Corp, College Station, Texas).

M. Plan for addressing confounding

Covariates have been selected (listed above) to adjust for potential confounding effects in the analysis stage of the study. Other confounders or potential sources of bias which have been identified are included within the exclusion criteria and are therefore addressed in the design of the study.

N. Plan for addressing missing data

We will censor patients; recording patients as not having had a study outcome event if nothing has been recorded or linked to by the end of the follow-up period (60 days in most of the study outcomes).

After clarifying whether there are important differences between individuals with complete and incomplete data, we will account for missing data either by using the multiple imputation method (for variables which seem to be missing at random; This will increase precision and validity of the findings), modelling or sensitivity analyses – choosing the method depending on whether the data is thought to be missing completely at random (MCAR), missing at random (MAT) or not.

O. Limitations of the study design, data sources and analytical methods

- CPRD contains routinely collected clinical data, the reported cases are therefore not collected for research purposes. We expect variations between GPs in coding diagnoses and some GPs may enter information as free text rather than coded. An absence of a Read code in CPRD is interpreted as the absence of the infection/outcome (i.e. positive predictive value will tend to be higher, sensitivity will be lower). Patients may fail to present to a GP at all, or may be delayed in presenting where an outcome may be seen. The data, for the reasons above, are therefore prone to coding errors, missing data, and misclassification of the occurrence and timing of the exposure and outcome. Defensive coding may cause diagnostic coding transfer to occur.
- Compliance and severity of illness are not collected in the data. We are not able to identify whether those treated with antibiotics may not have collected or completed their antibiotic prescription. We cannot examine whether patients who were prescribed an antibiotic may have been at greater risk of developing one of the outcomes of interest (indication bias).
- CPRD is a 6% sample of the national data, this could
- The CPRD database collects from volunteer practices, which make up a 6% sample of the national data. These are often larger practices thought to provide better quality of care. These limitations could make the study population less representative of the general population.
- Causal inference: It is difficult to ascertain whether a decrease in prescribing is due to change in guidance or to lowered incidence of particular infection and therefore the need to prescribe. Furthermore, it is difficult to identify the cause of the clinical outcome; an increase

in admission or higher mortality for a particular "secondary" infection may not have been related to the primary GP visit.

P. Patient of user group involvement (if applicable)

This project will be developed within a context of strong patient and public involvement, which has already been established within the University, the Trust and the AMR/HCAI Health Protection Research Unit (HPRU). In particular the strength of patient involvement within the Trust via its Patient Panels and "shadow foundation trust members" provides a pool of individuals willing to serve the patient interest in future initiatives, including becoming involved in health services research.

Two patients, Fran Husson and Tim Sims, who we are involved with the Centre for Infection Prevention and Management, have been consulted for being part of the project. These patients have been initially contacted via email, regular discussion have since been established. These individuals have experience contributing to research projects at steering/strategy group level. Ms Husson is involved in a Collaboration for Leadership in Applied Health Research and Care (CLAHRC) project, which aims to help patients with their medication and associated risks, such as antibiotic resistance and Mr Sims is a contributor to his local Healthwatch where he is much involved in Patient Lead Assessments of the Care Environment inspections.

The patient representatives, as active members of the research, have reviewed the project summary in plain English and the objectives. Their input has resulted in greater consideration of the patients' perspective in the process of managing the project.

Q. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

We will communicate our findings through Peer-reviewed publications and attendance at national, European and international conferences: International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), European Conference of Clinical Microbiology and Infectious Diseases (ECCMID), Federation of Infection Societies conferences (FIS), International Congress on Infectious Diseases (ICID, previously ISID), PHE annual conference and the society for Academic Primary Care (SAPC) conference. We aim to publish three main research papers in international peer reviewed journals with a high-impact factor.

We will present findings to the healthcare professionals, academics, patients and public (seminars, workshops, and awareness days) at events organised by Imperial College London and other partners. Specifically, aiming to present at the annual Healthcare Associated Infections/ Antimicrobial Resistance (HCAI/AMR) HPRU conference open to the public, patients, researchers, healthcare professionals, and Public Health England (PHE) staff.

We intend on reporting results through communications channels for the HPRU (HCAI/AMR Health Protection Research Unit): including updates to the HPRU HCAI and AMR website, the CIPM (Centre for Infection Prevention and Management) website (www.imperial.ac.uk/cipm), disseminated through newsletters to patients, researchers, healthcare professionals and key stakeholders (CIPM's newsletter is produced 4 times a year); public engagement events (e.g. the Imperial Festival) and networks involving patients and the public including organisations such as Healthwatch and the NWL CLAHRC.

R. References

1. Organisation WH. Fifty-first World Health Assembly. Emerging and other communicable diseases: Antimicrobial resistance. WHO. 1998;Agenda item 21.3(WHA51.17).
2. Davies S. Annual report of the chief medical officer. 2011. Vol 2. Infections and the rise of antimicrobial resistance. . Department of Health CMO Annual Report. 2013.
3. Davies S, Gibbens N. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. Department of Health, London. 2013.
4. Budd E. Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI): 5th Annual Report, April 2013-March 2014. Antimicrobial Resistance and Healthcare Associated Infection (ARHAI). 2014.
5. NHS_England. Quality Premium: 2015/16 guidance for CCGs2015. Available from: http://www.england.nhs.uk/wp-content/uploads/2015/04/qual-prem-guid-1516.pdf.
6. England PH. English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report. PHE. 2014.
7. Hawker JI, Smith S, Smith GE, Morbey R, Johnson AP, Fleming DM, et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. J Antimicrob Chemother. 2014;69(12):3423-30.
8. Roy R, Doshi N, Cullen M, Thornhill C, Birch M. Changing trends in community urinary tract infections in South Manchester. Clinical Microbiology and Infection. 2009;15:S163.
9. Petersen I, Hayward AC, Subgroup SS. Antibacterial prescribing in primary care. J Antimicrob Chemother. 2007;60 Suppl 1:i43-7.
10. Abdi H. Bonferroni and sidok correlations for multiple comparisons. In: Salkind IMJ, editor. Encyclopedia of Measurement and Statistics: Thousand Oaks (CA): Sage; 2007.

Appendix 18. CPRD Read code lists for initial extract of index infections (Chapter 3, Page 1 of 10)

Medcode	CPRD Clinical events	Read code	Read term	Diagnostic Group
38483	534	1492.00	H/O: chronic ear infection	Acute Otitis Media
5813	664760	1C3..00	Earache symptoms	Acute Otitis Media
5831	44202	1C32.00	Unilateral earache	Acute Otitis Media
6657	7037	1C33.00	Bilateral earache	Acute Otitis Media
16508	10550	1C3Z.00	Earache symptom NOS	Acute Otitis Media
6349	66946	1C4..00	Ear discharge symptoms	Acute Otitis Media
6655	12056	1C42.00	Ear discharge present	Acute Otitis Media
15896	1686	1C43.00	Blood discharge from ear	Acute Otitis Media
51775	1403	1C4Z.00	Ear discharge symptom NOS	Acute Otitis Media
6390	81672	2D6..00	O/E - discharge from ear	Acute Otitis Media
53325	160	2D62.00	O/E - serous ear discharge	Acute Otitis Media
16147	633	2D64.00	O/E - purulent ear discharge	Acute Otitis Media
42443	332	2D66.00	O/E - blood from ear	Acute Otitis Media
49511	244	2D6Z.00	O/E - ear discharge NOS	Acute Otitis Media
5806	116164	2D7..00	O/E - painful ear	Acute Otitis Media
37432	471	2D7Z.00	O/E - painful ear NOS	Acute Otitis Media
3096	15797	2D9..14	O/E - perforated tymp.membrane	Acute Otitis Media
24082	5497	2D94.00	O/E - tympanic membrane pink	Acute Otitis Media
18363	9330	2D95.00	O/E - tympanic membrane red	Acute Otitis Media
24798	2275	2D96.00	O/E -tympanic membrane bulging	Acute Otitis Media
25509	534	2D97.00	O/E-otoscopy:central perforat.	Acute Otitis Media
51537	200	2D98.00	O/E - otoscopy:posterior perf.	Acute Otitis Media
21714	133	2D99.00	O/E - tympanic membrane tear	Acute Otitis Media
6626	7154	2D9B.00	O/E - tympanic membr retracted	Acute Otitis Media
5903	2757	A552.00	Postmeasles otitis media	Acute Otitis Media
18107	1927	AB2y100	Candidal otitis externa	Acute Otitis Media
2138	969195	F501.00	Infective otitis externa	Acute Otitis Media
1242	32657	F501000	Unspecified infective otitis externa	Acute Otitis Media
14907	16862	F501100	Acute infective otitis externa	Acute Otitis Media
68242	17	F501400	Infective otitis externa due to erysipelas	Acute Otitis Media
27616	71	F501411	Erysipelas - otitis externa	Acute Otitis Media
67338	3	F501500	Infective otitis externa due to herpes simplex	Acute Otitis Media
16249	184	F501700	Infective otitis externa due to impetigo	Acute Otitis Media
17353	942	F501711	Impetigo - otitis externa	Acute Otitis Media
36760	1110	F501900	Other acute external ear infections	Acute Otitis Media
20815	138	F501B00	Chronic otitis externa due to aspergillosis	Acute Otitis Media
41601	26	F501C00	Chronic otitis externa due to moniliasis	Acute Otitis Media
46099	51	F501D00	Chronic mycotic otitis externa NOS	Acute Otitis Media
27669	291	F501E00	Other chronic infective otitis externa	Acute Otitis Media
8700	19867	F501F00	Chronic infective otitis externa NOS	Acute Otitis Media
26065	16	F501G00	Haemorrhagic otitis externa	Acute Otitis Media
41806	400	F501y00	Other specified infective otitis externa	Acute Otitis Media
41120	2234	F501z00	Infective otitis externa NOS	Acute Otitis Media
3350	145682	F502.00	Other otitis externa	Acute Otitis Media

31047	12	F502100	Acute radiation otitis externa	Acute Otitis Media
16234	22	F502200	Acute chemical otitis externa	Acute Otitis Media
24250	59	F502300	Other contact otitis externa	Acute Otitis Media
10254	3811	F502400	Acute eczematoid otitis extern	Acute Otitis Media
6218	7797	F502411	Eczema of external ear	Acute Otitis Media
25370	124	F502500	Other reactive otitis externa	Acute Otitis Media
29665	397	F502600	Other acute non infective otitis externa	Acute Otitis Media
1724	13353	F502700	Other chronic non infective otitis externa	Acute Otitis Media
630	894193	F502z00	Otitis externa NOS	Acute Otitis Media
5537	6680	F502z11	Inflammation ear external	Acute Otitis Media
5577	318883	F51..00	Nonsuppurative otitis media + eustachian tube disorders	Acute Otitis Media
5887	278937	F510.00	Acute non suppurative otitis media	Acute Otitis Media
18371	7736	F510000	Acute otitis media with effusion	Acute Otitis Media
5148	16934	F510011	Acute secretory otitis media	Acute Otitis Media
7730	18300	F510100	Acute serous otitis media	Acute Otitis Media
21012	750	F510200	Acute mucoid otitis media	Acute Otitis Media
15973	166	F510300	Acute sanguinous otitis media	Acute Otitis Media
70788	5	F510400	Acute allergic serous otitis media	Acute Otitis Media
104056	2	F510500	Acute allergic mucoid otitis media	Acute Otitis Media
63780	3	F510600	Acute allergic sanguinous otitis media	Acute Otitis Media
20374	7766	F510z00	Acute nonsuppurative otitis media NOS	Acute Otitis Media
6559	12793	F511.00	Chronic otitis media with effusion, serous	Acute Otitis Media
24742	1830	F511.11	Chronic secretory otitis media, serous	Acute Otitis Media
17308	1925	F511000	Chronic tubotympanic catarrh	Acute Otitis Media
35910	372	F511100	Serosanguinous chronic otitis media	Acute Otitis Media
3817	921	F511200	Bilateral chronic serous otitis	Acute Otitis Media
31353	522	F511300	Unilateral chronic serous otitis	Acute Otitis Media
33661	1853	F511z00	Chronic serous otitis media NOS	Acute Otitis Media
2686	7358	F512.00	Chronic otitis media with effusion, mucoid	Acute Otitis Media
354	116901	F512.11	Glue ear	Acute Otitis Media
1184	47345	F512.12	Chronic secretory otitis media, mucoid	Acute Otitis Media
5539	4618	F512000	Glue ear, unspecified	Acute Otitis Media
62905	47	F512100	Mucosanguinous chronic otitis media	Acute Otitis Media
20578	431	F512z00	Chronic mucoid otitis media NOS	Acute Otitis Media
34348	551	F513.00	Chronic otitis media with effusion, other	Acute Otitis Media
37597	80	F513000	Chronic allergic otitis media	Acute Otitis Media
25188	192	F513100	Chronic otitis media with effusion, purulent	Acute Otitis Media
9993	118	F513111	Chronic secretory otitis media, purulent	Acute Otitis Media
26085	371	F513z00	Other chronic nonsuppurative otitis media NOS	Acute Otitis Media
17772	955	F514.00	Unspecified nonsuppurative otitis media	Acute Otitis Media
29845	48	F514000	Allergic otitis media NOS	Acute Otitis Media
5102	9016	F514100	Serous otitis media NOS	Acute Otitis Media
5390	26302	F514200	Catarrhal otitis media NOS	Acute Otitis Media
21749	138	F514300	Mucoid otitis media NOS	Acute Otitis Media
21725	3858	F514z00	Nonsuppurative otitis media NOS	Acute Otitis Media
16121	4349	F515.00	Eustachian tube salpingitis	Acute Otitis Media
7479	41572	F515.11	Catarrh - eustachian	Acute Otitis Media
67441	28	F515000	Unspecified eustachian tube salpingitis	Acute Otitis Media

62907	58	F515100	Acute eustachian tube salpingitis	Acute Otitis Media
69893	26	F515200	Chronic eustachian tube salpingitis	Acute Otitis Media
65039	125	F515z00	Eustachian tube salpingitis NOS	Acute Otitis Media
17160	10554	F516.00	Eustachian tube obstruction	Acute Otitis Media
2130	30009	F516.11	Block - eustachian tube	Acute Otitis Media
21513	121	F516000	Unspecified eustachian tube obstruction	Acute Otitis Media
71089	3	F516200	Cartilaginous eustachian tube obstruction	Acute Otitis Media
29867	446	F516z00	Eustachian tube obstruction NOS	Acute Otitis Media
38116	109	F517.00	Patulous eustachian tube	Acute Otitis Media
10517	3044	F518.00	Chronic otitis media with effusion, unspecified	Acute Otitis Media
535	329191	F51y000	Eustachian tube dysfunction	Acute Otitis Media
1474	286256	F52..00	Suppurative and unspecified otitis media	Acute Otitis Media
2137	83046	F520.00	Acute suppurative otitis media	Acute Otitis Media
10781	1846	F520000	Acute suppurative otitis media tympanic membrane intact	Acute Otitis Media
20669	1249	F520100	Acute suppurative otitis media tympanic membrane ruptured	Acute Otitis Media
61497	7	F520300	Acute suppurative otitis media due to disease EC	Acute Otitis Media
20372	4587	F520z00	Acute suppurative otitis media NOS	Acute Otitis Media
17866	1914	F521.00	Chronic suppurative otitis media, tubotympanic	Acute Otitis Media
24590	307	F522.00	Chronic suppurative otitis media, atticoantral	Acute Otitis Media
1376	21645	F523.00	Chronic suppurative otitis media NOS	Acute Otitis Media
15568	1978	F524.00	Purulent otitis media NOS	Acute Otitis Media
20871	1002	F524000	Bilateral suppurative otitis media	Acute Otitis Media
9973	10308	F525.00	Recurrent acute otitis media	Acute Otitis Media
3694	142714	F526.00	Acute left otitis media	Acute Otitis Media
4348	150314	F527.00	Acute right otitis media	Acute Otitis Media
1134	54093	F528.00	Acute bilateral otitis media	Acute Otitis Media
267	1509352	F52z.00	Otitis media NOS	Acute Otitis Media
1513	138280	F52z.11	Infection ear	Acute Otitis Media
21076	696	F54..00	Other tympanic membrane disorder	Acute Otitis Media
20115	603	F540100	Unspecified acute tympanitis	Acute Otitis Media
1707	39455	F542.00	Tympanic membrane perforation	Acute Otitis Media
624	64035	F542.11	Ear drum perforation	Acute Otitis Media
38807	553	F542000	Unspecified tympanic membrane perforation	Acute Otitis Media
33780	1300	F542100	Tympanic membrane central perforation	Acute Otitis Media
28128	593	F542200	Tympanic membrane attic perforation	Acute Otitis Media
20577	79	F542300	Other marginal tympanic membrane perforation	Acute Otitis Media
62962	12	F542400	Tympanic membrane with multiple perforations	Acute Otitis Media
54708	62	F542500	Tympanic membrane perforation, more than 50 %	Acute Otitis Media
68681	11	F542511	Tympanic membrane - total perforation	Acute Otitis Media
32763	81	F542600	Tympanic membrane perforation, less than 50 %	Acute Otitis Media
29755	1176	F542z00	Tympanic membrane perforation NOS	Acute Otitis Media
47486	56	F54y.00	Other tympanic membrane disorder	Acute Otitis Media
20731	207	F54y000	Healed tympanic membrane perforation	Acute Otitis Media
21898	1061	F54y300	Retraction of tympanic membrane	Acute Otitis Media
31523	61	F54yz00	Other tympanic membrane disorder NOS	Acute Otitis Media
35779	161	F54z.00	Tympanic membrane disorder NOS	Acute Otitis Media
638	103241	F586.00	Otorrhoea	Acute Otitis Media

16244	379	F586000	Unspecified otorrhoea	Acute Otitis Media
6415	7899	F586011	Discharging ear NOS	Acute Otitis Media
15510	444	F586z00	Otorrhoea NOS	Acute Otitis Media
731	583578	F587.00	Otalgia	Acute Otitis Media
1135	617323	F587.11	Ear pain	Acute Otitis Media
25171	1329	F587000	Unspecified otalgia	Acute Otitis Media
15826	427	F587100	Otogenic pain	Acute Otitis Media
33549	633	F587200	Referred ear pain	Acute Otitis Media
44481	3760	F587z00	Otalgia NOS	Acute Otitis Media
52749	26	FyuN000	[X]Other infective otitis externa	Acute Otitis Media
52118	262	FyuN100	[X]Other otitis externa	Acute Otitis Media
101532	3	FyuN300	[X]Otitis externa in bacterial diseases CE	Acute Otitis Media
99387	2	FyuN400	[X]Otitis externa in viral diseases classified elsewhere	Acute Otitis Media
72588	3	FyuN500	[X]Otitis externa in mycoses	Acute Otitis Media
73102	47	FyuN700	[X]Otitis externa in other diseases classified elsewhere	Acute Otitis Media
99403	8	FyuP000	[X]Other acute nonsuppurative otitis media	Acute Otitis Media
53734	20	FyuP200	[X]Other chronic suppurative otitis media	Acute Otitis Media
98656	5	FyuP300	[X]Otitis media in bacterial diseases classified elsewhere	Acute Otitis Media
72916	6	FyuP400	[X]Otitis media in viral diseases classified elsewhere	Acute Otitis Media
72914	18	FyuP500	[X]Otitis media in other diseases classified elsewhere	Acute Otitis Media
73271	2	FyuP800	[X]Other marginal perforations of tympanic membrane	Acute Otitis Media
52823	65	FyuP900	[X]Other perforations of tympanic membrane	Acute Otitis Media
73949	3	FyuPA00	[X]Other specified disorders of tympanic membrane	Acute Otitis Media
98629	2	FyuPE00	[X]Other specified disorders/middle ear+mastoid/diseases CE	Acute Otitis Media
46709	438	SN30.11	Aero-otitis media	Acute Otitis Media
243	772890	H01..11	Sinusitis	Rhinosinusitis
980	1093985	H01..00	Acute sinusitis	Rhinosinusitis
1309	40938	H1y1z14	Nasal infection	Rhinosinusitis
1674	1252	H132.00	Chronic ethmoidal sinusitis	Rhinosinusitis
2097	21958	H1y1z00	Nasal cavity and sinus disease NOS	Rhinosinusitis
2233	500	H13y100	Pansinusitis	Rhinosinusitis
2255	19781	H1y1z15	Sore nostril	Rhinosinusitis
2257	115353	H13..00	Chronic sinusitis	Rhinosinusitis
2984	12305	H131.11	Frontal sinusitis	Rhinosinusitis
3110	155846	H1y1z12	Nasal congestion	Rhinosinusitis
3624	26615	H130.12	Maxillary sinusitis	Rhinosinusitis
3716	11998	1B1G000	Sinus headache	Rhinosinusitis
3821	86755	H00..16	Rhinitis - acute	Rhinosinusitis
4433	4108	H130.00	Chronic maxillary sinusitis	Rhinosinusitis
4722	3520	H1y1.13	Sinus disease NOS	Rhinosinusitis
5437	34716	H13z.00	Chronic sinusitis NOS	Rhinosinusitis
5754	220372	1BA5.11	Pain in sinuses	Rhinosinusitis
6386	4045	2DA2.00	O/E-maxillary sinus tenderness	Rhinosinusitis
7021	32016	H010.00	Acute maxillary sinusitis	Rhinosinusitis

7127	9470	1CC..00	Blocked sinuses	Rhinosinusitis
8213	15007	H011.00	Acute frontal sinusitis	Rhinosinusitis
9483	42087	H1y1z13	Sinus congestion	Rhinosinusitis
10546	9022	H13..11	Chronic rhinosinusitis	Rhinosinusitis
12017	6222	1BA9.00	Sinus headache	Rhinosinusitis
12759	2851	2DA3.00	O/E - frontal sinus tenderness	Rhinosinusitis
14788	2306	H1y1.00	Other nasal cavity and sinus disease	Rhinosinusitis
15163	2356	H131.00	Chronic frontal sinusitis	Rhinosinusitis
15724	1028	H012.00	Acute ethmoidal sinusitis	Rhinosinusitis
17173	6100	H135.00	Recurrent sinusitis	Rhinosinusitis
18572	1087	H17..12	Allergic rhinosinusitis	Rhinosinusitis
19284	580	H01y000	Acute pansinusitis	Rhinosinusitis
29696	133	H01y.00	Other acute sinusitis	Rhinosinusitis
33437	220	H130.11	Antritis - chronic	Rhinosinusitis
33664	28209	H01z.00	Acute sinusitis NOS	Rhinosinusitis
45181	19	Hyu2400	[X]Other specified disorders of nose and nasal sinuses	Rhinosinusitis
48703	34	H133.00	Chronic sphenoidal sinusitis	Rhinosinusitis
60733	55	H01yz00	Other acute sinusitis NOS	Rhinosinusitis
63733	16	Hyu2200	[X]Other chronic sinusitis	Rhinosinusitis
94218	3781	H014.00	Acute rhinosinusitis	Rhinosinusitis
97330	23	Hyu0000	[X]Other acute sinusitis	Rhinosinusitis
142	296801	H040.00	Acute laryngitis	Sore throat
310	354736	H02..13	Throat infection - pharyngitis	Sore throat
404	1302622	1C9..11	Throat soreness	Sore throat
407	187705	H02z.00	Acute pharyngitis NOS	Sore throat
892	1012	H043z00	Acute epiglottitis NOS	Sore throat
893	755624	H02..00	Acute pharyngitis	Sore throat
1285	12955	H042.11	Laryngotracheitis	Sore throat
1765	24941	A340.00	Streptococcal sore throat	Sore throat
3260	75330	H00..00	Acute nasopharyngitis	Sore throat
4276	3539	H160400	Laryngitis sicca	Sore throat
4902	8936	A340200	Streptococcal pharyngitis	Sore throat
5553	47721	1C92.00	Has a sore throat	Sore throat
5755	2262536	1C9..00	Sore throat symptom	Sore throat
6014	135391	H02..11	Sore throat NOS	Sore throat
6173	123	H16z.00	Chronic laryngitis NOS	Sore throat
7318	285	H161.00	Chronic laryngotracheitis	Sore throat
8480	2371	J083600	Uvulitis	Sore throat
8496	23265	A340300	Streptococcal tonsillitis	Sore throat
10087	15414	H042.00	Acute laryngotracheitis	Sore throat
10641	1239	H043.00	Acute epiglottitis (non strep)	Sore throat
10765	863	H040200	Acute catarrhal laryngitis	Sore throat
11942	833	H16..00	Chronic laryngitis and laryngotracheitis	Sore throat
12489	2049	1C93.00	Persistent sore throat	Sore throat
14931	71304	2DC3.00	Inflamed throat	Sore throat
15039	3151	R041.00	[D]Throat pain	Sore throat
15231	6304	H160.00	Chronic laryngitis	Sore throat
15287	13019	1C9Z.00	Sore throat symptom NOS	Sore throat

16120	257	H04z.00	Acute laryngitis and tracheitis NOS	Sore throat
16217	351	A340z00	Streptococcal sore throat NOS	Sore throat
16718	186	A340100	Streptococcal laryngitis	Sore throat
17513	2030	H160100	Chronic catarrhal laryngitis	Sore throat
17899	2161	H023.00	Acute bacterial pharyngitis	Sore throat
20104	49876	H03z.00	Acute tonsillitis NOS	Sore throat
22720	3689	H040z00	Acute laryngitis NOS	Sore throat
24471	457	H042z00	Acute laryngotracheitis NOS	Sore throat
25259	153	H042000	Acute laryngotracheitis without obstruction	Sore throat
25436	59	H160000	Chronic simple laryngitis	Sore throat
29589	47	H023100	Acute staphylococcal pharyngitis	Sore throat
31501	110	H040300	Acute phlegmonous laryngitis	Sore throat
32834	281	H160500	Congested larynx	Sore throat
38128	221	H043200	Acute obstructive laryngitis	Sore throat
41268	116	H160z00	Chronic laryngitis NOS	Sore throat
41324	4115	H04..00	Acute laryngitis and tracheitis	Sore throat
49839	33	H160200	Chronic hypertrophic laryngitis	Sore throat
52756	55	H040x00	Acute bacterial laryngitis unspecified	Sore throat
53395	173	H023z00	Acute bacterial pharyngitis NOS	Sore throat
65650	24	H043000	Acute epiglottitis without obstruction	Sore throat
69898	14	H042100	Acute laryngotracheitis with obstruction	Sore throat
73546	2	H160300	Chronic atrophic laryngitis	Sore throat
92428	18	H023000	Acute pneumococcal pharyngitis	Sore throat
76	4517093	H05z.00	Upper respiratory infection NOS	Upper RTI
92	5380543	171..00	Cough	Upper RTI
138	2741842	H03..00	Acute tonsillitis	Upper RTI
292	865531	1719.00	Chesty cough	Upper RTI
293	916163	H06z111	Respiratory tract infection	Upper RTI
386	39528	1CB3.00	Throat pain	Upper RTI
1160	482767	R062.00	[D]Cough	Upper RTI
1234	137915	1716.00	Productive cough NOS	Upper RTI
1273	3647923	171..11	C/O - cough	Upper RTI
1499	14675	1CB5.00	Throat irritation	Upper RTI
1612	18950	171A.00	Chronic cough	Upper RTI
1747	50563	H037.00	Recurrent acute tonsillitis	Upper RTI
2125	206622	H03..12	Tonsillitis	Upper RTI
2637	2757537	H05z.11	Upper respiratory tract infection NOS	Upper RTI
3628	81287	171B.00	Persistent cough	Upper RTI
3645	14547	1716.11	Coughing up phlegm	Upper RTI
4061	26327	H031.00	Acute follicular tonsillitis	Upper RTI
4221	12780	H054.00	Recurrent upper respiratory tract infection	Upper RTI
4718	4171	H055.00	Pharyngolaryngitis	Upper RTI
4931	206977	1712.00	Dry cough	Upper RTI
6294	441094	H051.00	Acute upper respiratory tract infection	Upper RTI
7074	28956	H5yy.11	Respiratory infection NOS	Upper RTI
7366	4829	1CB3.11	Pain in throat	Upper RTI
7706	52716	1713.00	Productive cough -clear sputum	Upper RTI
7707	22491	171Z.00	Cough symptom NOS	Upper RTI

7708	49402	1715.00	Productive cough-yellow sputum	Upper RTI
7773	131028	1714.00	Productive cough -green sputum	Upper RTI
8025	228705	H0...00	Acute respiratory infections	Upper RTI
8452	780	H032.00	Acute ulcerative tonsillitis	Upper RTI
9807	19853	171..12	Sputum - symptom	Upper RTI
10093	572	H053.00	Tracheopharyngitis	Upper RTI
10156	12187	H035.00	Acute bacterial tonsillitis	Upper RTI
11499	18570	H03..11	Throat infection - tonsillitis	Upper RTI
12010	2329	H030.00	Acute erythematous tonsillitis	Upper RTI
15410	6289	1CBZ.00	Throat symptom NOS	Upper RTI
15628	2023	H05y.00	Other upper respiratory infections of multiple sites	Upper RTI
15970	418	H035z00	Acute bacterial tonsillitis NOS	Upper RTI
18238	507	H141.12	Enlargement of tonsil or adenoid	Upper RTI
18907	2538	171F.00	Cough with fever	Upper RTI
18908	1288	H050.00	Acute laryngopharyngitis	Upper RTI
21113	63742	H0z..00	Acute respiratory infection NOS	Upper RTI
21415	5696	H052.00	Pharyngotracheitis	Upper RTI
22396	4629	2DC1.11	O/E - fauces injected	Upper RTI
23640	957	H0y..00	Other specified acute respiratory infections	Upper RTI
24664	11951	2DC1.00	O/E - pharynx hyperaemic	Upper RTI
26010	14411	H05..00	Other acute upper respiratory infections	Upper RTI
53055	61	Hyu0.00	[X]Acute upper respiratory infections	Upper RTI
73118	79	Hyu0200	[X]Acute tonsillitis due to other specified organisms	Upper RTI
90332	172	171K.00	Barking cough	Upper RTI
68	2850610	H06z011	Chest infection	Lower RTI
148	434614	H30..00	Bronchitis unspecified	Lower RTI
152	69735	H302.00	Wheezy bronchitis	Lower RTI
312	802035	H060.00	Acute bronchitis	Lower RTI
763	31328	A33..00	Whooping cough	Lower RTI
978	89593	H51..00	Pleurisy	Lower RTI
1019	173369	H061.00	Acute bronchiolitis	Lower RTI
1025	13790	1719.11	Bronchial cough	Lower RTI
1142	195711	H044.00	Croup	Lower RTI
1257	226426	H041.00	Acute tracheitis	Lower RTI
1446	184287	H312200	Acute exacerbation of chronic obstructive airways disease	Lower RTI
1934	4161	H301.00	Laryngotracheobronchitis	Lower RTI
2476	27888	H07..00	Chest cold	Lower RTI
2581	1889094	H06z000	Chest infection NOS	Lower RTI
3163	12060	H300.00	Tracheobronchitis NOS	Lower RTI
3243	24697	H31..00	Chronic bronchitis	Lower RTI
3358	271290	H06z100	Lower resp tract infection	Lower RTI
3480	14611	H30z.00	Bronchitis NOS	Lower RTI
3842	8495	A330.00	Bordetella pertussis	Lower RTI
4899	12130	H06z200	Recurrent chest infection	Lower RTI
5798	1698	H312000	Chronic asthmatic bronchitis	Lower RTI
5909	476	H312011	Chronic wheezy bronchitis	Lower RTI
5978	124635	H060.11	Acute wheezy bronchitis	Lower RTI

6124	129383	H062.00	Acute lower respiratory tract infection	Lower RTI
6181	71	H061400	Obliterating fibrous bronchiolitis	Lower RTI
7092	3504	H30..12	Recurrent wheezy bronchitis	Lower RTI
9043	365	H060600	Acute pneumococcal bronchitis	Lower RTI
11072	1793	H060300	Acute purulent bronchitis	Lower RTI
11101	7859	H060500	Acute tracheobronchitis	Lower RTI
11150	330	H311.00	Mucopurulent chronic bronchitis	Lower RTI
12476	404	H041000	Acute tracheitis without obstruction	Lower RTI
14798	1181	H312100	Emphysematous bronchitis	Lower RTI
15157	3522	H31z.00	Chronic bronchitis NOS	Lower RTI
15626	1685	H310000	Chronic catarrhal bronchitis	Lower RTI
15761	199	A331.00	Bordetella parapertussis	Lower RTI
16313	5555	H041z00	Acute tracheitis NOS	Lower RTI
17185	1717	H061200	Acute bronchiolitis with bronchospasm	Lower RTI
17359	3192	H30..11	Chest infection - unspecified bronchitis	Lower RTI
17917	2551	H061z00	Acute bronchiolitis NOS	Lower RTI
18207	680	H33zz13	Allergic bronchitis NEC	Lower RTI
18451	768	H061500	Acute bronchiolitis due to respiratory syncytial virus	Lower RTI
19400	621	H26..11	Chest infection - pnemonia due to unspecified organism	Lower RTI
19431	8207	H043211	Croup	Lower RTI
20198	9644	H060z00	Acute bronchitis NOS	Lower RTI
21061	4474	H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn	Lower RTI
21145	1145	H060400	Acute croupous bronchitis	Lower RTI
23482	382	H510.00	Pleurisy without effusion or active tuberculosis	Lower RTI
23618	813	H31y000	Chronic tracheitis	Lower RTI
24248	28	H313.00	Mixed simple and mucopurulent chronic bronchitis	Lower RTI
24316	58	H24..11	Chest infection with infectious disease EC	Lower RTI
24800	134	H060x00	Acute bacterial bronchitis unspecified	Lower RTI
25603	630	H310.00	Simple chronic bronchitis	Lower RTI
26125	174	H312300	Bronchiolitis obliterans	Lower RTI
27819	1089	H312.00	Obstructive chronic bronchitis	Lower RTI
29669	13342	H06..00	Acute bronchitis and bronchiolitis	Lower RTI
30509	451	SP13200	Post operative chest infection	Lower RTI
31603	1	H510A00	Staphylococcal pleurisy	Lower RTI
31645	126	H510z00	Pleurisy without effusion or active tuberculosis NOS	Lower RTI
31689	77	H511.00	Bacterial pleurisy with effusion	Lower RTI
31886	186	H060A00	Acute bronchitis due to mycoplasma pneumoniae	Lower RTI
32818	50	H510900	Pneumococcal pleurisy	Lower RTI
37447	5118	H06z112	Acute lower respiratory tract infection	Lower RTI
37959	4	H311100	Fetid chronic bronchitis	Lower RTI
38639	33	H460.00	Bronchitis and pneumonitis due to chemical fumes	Lower RTI
40159	50	H311000	Purulent chronic bronchitis	Lower RTI
41137	652	H06z.00	Acute bronchitis or bronchiolitis NOS	Lower RTI
41589	149	H061100	Acute obliterating bronchiolitis	Lower RTI
42548	928	A33z.00	Whooping cough NOS	Lower RTI

43345	35	H511000	Pneumococcal pleurisy with effusion	Lower RTI
43362	16	H060700	Acute streptococcal bronchitis	Lower RTI
44525	68	H312z00	Obstructive chronic bronchitis NOS	Lower RTI
44842	17	H511z00	Bacterial pleurisy with effusion NOS	Lower RTI
45089	58	H31y100	Chronic tracheobronchitis	Lower RTI
49794	19	H060900	Acute neisseria catarrhalis bronchitis	Lower RTI
50396	30	H060000	Acute fibrinous bronchitis	Lower RTI
54533	6	H061000	Acute capillary bronchiolitis	Lower RTI
54830	16	H460000	Acute bronchitis due to chemical fumes	Lower RTI
55391	76	H060v00	Subacute bronchitis unspecified	Lower RTI
55758	4	H460z00	Bronchitis and pneumonitis due to chemical fumes NOS	Lower RTI
59587	12	H501600	Pyothorax	Lower RTI
61118	37	H310z00	Simple chronic bronchitis NOS	Lower RTI
61513	28	H311z00	Mucopurulent chronic bronchitis NOS	Lower RTI
65916	2	H060F00	Acute bronchitis due to echovirus	Lower RTI
66043	23	H31y.00	Other chronic bronchitis	Lower RTI
66228	29	H061600	Acute bronchiolitis due to other specified organisms	Lower RTI
66397	73	Hyu1.00	[X]Other acute lower respiratory infections	Lower RTI
67278	17	Hyu3.00	[X]Chronic lower respiratory diseases	Lower RTI
68066	18	H31yz00	Other chronic bronchitis NOS	Lower RTI
68867	54	H041100	Acute tracheitis with obstruction	Lower RTI
69192	19	H061300	Acute exudative bronchiolitis	Lower RTI
69352	1	H510B00	Streptococcal pleurisy	Lower RTI
71370	13	H060200	Acute pseudomembranous bronchitis	Lower RTI
73100	12	Hyu1000	[X]Acute bronchitis due to other specified organisms	Lower RTI
93010	2	H511100	Staphylococcal pleurisy with effusion	Lower RTI
93153	3	H060B00	Acute bronchitis due to coxsackievirus	Lower RTI
99214	3	Hyu1100	[X]Acute bronchiolitis due to other specified organisms	Lower RTI
101775	2	H060100	Acute membranous bronchitis	Lower RTI
108784	1	H511200	Streptococcal pleurisy with effusion	Lower RTI
368	157731	H00..11	Common cold	Viral RTI
556	276478	H27..00	Influenza	Viral RTI
896	154582	H00..14	Nasal catarrh - acute	Viral RTI
1246	256922	H00..12	Coryza - acute	Viral RTI
1382	6442	H060w00	Acute viral bronchitis unspecified	Viral RTI
2157	527670	H27z.11	Flu like illness	Viral RTI
4868	34266	H024.00	Acute viral pharyngitis	Viral RTI
5115	5705	H040w00	Acute viral laryngitis unspecified	Viral RTI
5947	11054	H27z.12	Influenza like illness	Viral RTI
6421	197259	H05z.12	Viral upper respiratory tract infection NOS	Viral RTI
6466	28545	H02..12	Viral sore throat NOS	Viral RTI
6620	5161	H00..13	Febrile cold	Viral RTI
7714	2667	A3B5.00	Haemophilus influenzae infection	Viral RTI
8950	24191	1656.00	Feverish cold	Viral RTI
8980	19388	16L..00	Influenza-like symptoms	Viral RTI

9093	9864	H00..15	Pyrexial cold	Viral RTI
9357	10722	H036.00	Acute viral tonsillitis	Viral RTI
14791	2901	H27y100	Influenza with gastrointestinal tract involvement	Viral RTI
15774	384	H271000	Influenza with laryngitis	Viral RTI
16388	40663	H27z.00	Influenza NOS	Viral RTI
21492	83	H060800	Acute haemophilus influenzae bronchitis	Viral RTI
23488	2259	H271z00	Influenza with respiratory manifestations NOS	Viral RTI
29273	830	H060C00	Acute bronchitis due to parainfluenza virus	Viral RTI
29617	463	H271100	Influenza with pharyngitis	Viral RTI
31363	22	H27yz00	Influenza with other manifestations NOS	Viral RTI
43317	29	H040400	Acute haemophilus influenzae laryngitis	Viral RTI
43625	1082	H271.00	Influenza with other respiratory manifestation	Viral RTI
47472	127	H27y.00	Influenza with other manifestations	Viral RTI
48593	28	H060D00	Acute bronchitis due to respiratory syncytial virus	Viral RTI
64890	29	H060E00	Acute bronchitis due to rhinovirus	Viral RTI
94930	6	H29..00	Avian influenza	Viral RTI
98102	3996	H2A..11	Influenza A (H1N1) swine flu	Viral RTI
98115	2922	1J72.11	Suspected swine influenza	Viral RTI
98125	710	1J72.00	Suspected influenza A virus subtype H1N1 infection	Viral RTI
105895	8	H061700	Acute bronchiolitis due to human metapneumovirus	Viral RTI

Appendix 19. CPRD Read code lists of the complications assessed (Chapter 3, Page 1 of 10)

Medcode	Clinical events	Read code	Read term	Outcome Group
885	23579	A38..00	Septicaemia	Bloodstream infection
1703	2627	A362.00	Meningococcal septicaemia	Bloodstream infection
2136	26843	A38z.11	Sepsis	Bloodstream infection
3613	1680	Q40A.00	Sepsis of the newborn	Bloodstream infection
7781	19	L403.00	Puerperal septicaemia	Bloodstream infection
7787	647	A382.00	Pneumococcal septicaemia	Bloodstream infection
10872	566	A384200	Escherichia coli septicaemia	Bloodstream infection
10978	168	A380100	Septicaemia due to streptococcus, group B	Bloodstream infection
11690	236	L40..11	Sepsis - puerperal	Bloodstream infection
12400	118	A384300	Pseudomonas septicaemia	Bloodstream infection
12578	80	A380400	Septicaemia due to enterococcus	Bloodstream infection
15229	737	A380.00	Streptococcal septicaemia	Bloodstream infection
16104	909	A381.00	Staphylococcal septicaemia	Bloodstream infection
18191	861	R106.00	[D]Unspecified bacteraemia	Bloodstream infection
22031	180	Q40y200	Septicaemia of newborn	Bloodstream infection
23079	138	R055511	[D]Septicaemic shock	Bloodstream infection
23991	437	A384211	E.coli septicaemia	Bloodstream infection
25895	92	A380300	Septicaemia due to streptococcus pneumoniae	Bloodstream infection
28610	93	A384100	Haemophilus influenzae septicaemia	Bloodstream infection
29950	73	A380000	Septicaemia due to streptococcus, group A	Bloodstream infection
30102	168	A381000	Septicaemia due to Staphylococcus aureus	Bloodstream infection
31517	113	A384000	Gram negative septicaemia NOS	Bloodstream infection
31706	27	A383.00	Septicaemia due to anaerobes	Bloodstream infection
33765	1217	A38z.00	Septicaemia NOS	Bloodstream infection
35232	216	A384.00	Septicaemia due to other gram negative organisms	Bloodstream infection
39691	71	Q40A000	Sepsis of newborn due to Staphylococcus aureus	Bloodstream infection
42825	21	A381100	Septicaemia due to coagulase-negative staphylococcus	Bloodstream infection
47693	73	Q40W.00	Sepsis of newborn due to other+unspecified streptococci	Bloodstream infection
49590	16	A380500	Vancomycin resistant enterococcal septicaemia	Bloodstream infection
53182	178	A38y.00	Other specified septicaemias	Bloodstream infection
53762	38	Ayu3J00	[X]Septicaemia, unspecified	Bloodstream infection
54077	15	H5y0100	Tracheostomy sepsis	Bloodstream infection
54534	13	A384400	Serratia septicaemia	Bloodstream infection
56336	23	Q40A100	Sepsis of newborn due to Escherichia coli	Bloodstream infection
72106	1	Ayu3H00	[X]Other specified septicaemia	Bloodstream infection
72876	7	A384z00	Other gram negative septicaemia NOS	Bloodstream infection
72881	2	Ayu3G00	[X]Septicaemia due to other gram-negative organisms	Bloodstream infection
93976	13	Qyu4200	[X]Other bacterial sepsis of newborn	Bloodstream infection
97485	1	L403000	Puerperal septicaemia unspecified	Bloodstream infection
98366	3	Qyu4800	[X]Sepsis of newborn due to other+unspecified streptococci	Bloodstream infection
98545	7	Ayu3F00	[X]Streptococcal septicaemia, unspecified	Bloodstream infection
98669	1	Qyu4100	[X]Sepsis/newborn due to other+unspecified staphylococcus	Bloodstream infection
101759	2	Ayu3E00	[X]Other streptococcal septicaemia	Bloodstream infection
104028	8697	A3C..00	Sepsis	Bloodstream infection

104150	283	A3Cy.00	Other specified sepsis	Bloodstream infection
104189	16	A3C0100	Sepsis due to Streptococcus group B	Bloodstream infection
104260	303	A3Cz.00	Sepsis NOS	Bloodstream infection
104294	2	A396.00	Sepsis due to Actinomyces	Bloodstream infection
104315	9	A3C0300	Sepsis due to Streptococcus pneumoniae	Bloodstream infection
104492	15	A3C1000	Sepsis due to Staphylococcus aureus	Bloodstream infection
104577	22	A3C1.00	Sepsis due to Staphylococcus	Bloodstream infection
104633	20	A3C2.11	Sepsis due to anaerobes	Bloodstream infection
104731	13	A3C0000	Sepsis due to Streptococcus group A	Bloodstream infection
104900	3	A3C0y00	Other streptococcal sepsis	Bloodstream infection
105053	2	A3C3y00	Sepsis due to other Gram negative organisms	Bloodstream infection
105075	33	A3C3.00	Sepsis due to Gram negative bacteria	Bloodstream infection
105102	5	A3C2.00	Sepsis due to anaerobic bacteria	Bloodstream infection
105423	9	A3C0.00	Sepsis due to Streptococcus	Bloodstream infection
105716	6	A3C0z00	Streptococcal sepsis, unspecified	Bloodstream infection
106405	738	1JN0.00	Suspected sepsis	Bloodstream infection
108045	2	A3C3.11	Sepsis due to Gram negative organisms	Bloodstream infection
110079	1	Q40A200	Sepsis of newborn due to anaerobes	Bloodstream infection
110225	1	A3C1z00	Sepsis due to staphylococcus NOS	Bloodstream infection
442	5933	A360.00	Meningococcal meningitis	Brain abscesses & meningitis
2386	7929	F02z.00	Unspecified meningitis	Brain abscesses & meningitis
2845	1396	F000.00	Haemophilus meningitis	Brain abscesses & meningitis
3945	4483	F02..00	Meningitis of unspecified cause	Brain abscesses & meningitis
4396	290	F002.00	Streptococcal meningitis	Brain abscesses & meningitis
4605	1741	F001.00	Pneumococcal meningitis	Brain abscesses & meningitis/Pneumonia
6838	4754	F00..00	Bacterial meningitis	Brain abscesses & meningitis
8095	31	F040400	Extradural intracranial abscess	Brain abscesses & meningitis
11736	970	F005.00	Meningitis - meningococcal	Brain abscesses & meningitis
11975	572	A130.00	Tuberculous meningitis	Brain abscesses & meningitis
11976	225	F004.00	Meningitis - tuberculous	Brain abscesses & meningitis
11987	564	F040011	Cerebral abscess	Brain abscesses & meningitis
15977	728	A42z.11	Aseptic meningitis	Brain abscesses & meningitis
21936	433	A365.00	Meningococcal meningitis with acute meningococcal septicaem	Brain abscesses & meningitis/BSI
23466	24	F04z.00	Intracranial or intraspinal abscess NOS	Brain abscesses & meningitis
24577	607	A366.00	Meningococcal meningitis with meningococcal septicaemia	Brain abscesses & meningitis/BSI
27466	411	F040.11	Brain abscess	Brain abscesses & meningitis
27627	770	F01..00	Meningitis due to other organisms	Brain abscesses & meningitis
28567	47	F04..00	Intracranial and intraspinal abscesses	Brain abscesses & meningitis
31091	214	F04z000	Epidural abscess	Brain abscesses & meningitis
31466	51	F040511	Subdural intracranial abscess	Brain abscesses & meningitis
31480	140	7004000	Drainage of abscess of brain tissue	Brain abscesses & meningitis
34412	117	F01z.00	Meningitis due to organism NOS	Brain abscesses & meningitis
40088	5	F01y000	Meningitis due to leptospira	Brain abscesses & meningitis
40669	55	7008100	Aspiration of abscess of brain tissue	Brain abscesses & meningitis
40670	86	F040111	Cerebellar abscess	Brain abscesses & meningitis
42438	36	F04X.00	Extradural and subdural abscess, unspecified	Brain abscesses & meningitis
42699	65	F00y211	Meningitis due to escherichia coli	Brain abscesses & meningitis
45875	9	F040211	Otogenic intracranial abscess	Brain abscesses & meningitis
46388	30	F00y212	Escherichia coli meningitis	Brain abscesses & meningitis
48104	100	F040.00	Intracranial abscess	Brain abscesses & meningitis
48106	27	F020.00	Nonpyogenic meningitis	Brain abscesses & meningitis
49454	8	F013.00	Meningitis due to sarcoidosis	Brain abscesses & meningitis
49633	21	F022.00	Chronic meningitis	Brain abscesses & meningitis

50303	20	F003.00	Staphylococcal meningitis	Brain abscesses & meningitis
50688	2	F040300	Epidural intracranial abscess	Brain abscesses & meningitis
52479	28	F00y200	Meningitis due to escherichia coli	Brain abscesses & meningitis
52697	3	F00y611	Pseudomonas meningitis	Brain abscesses & meningitis
53443	3	F040200	Otogenic intracranial abscess	Brain abscesses & meningitis
54908	14	F040600	Tuberculous intracranial abscess	Brain abscesses & meningitis
54980	10	F040500	Subdural intracranial abscess	Brain abscesses & meningitis
56366	3	F007800	Meningitis due to pertussis	Brain abscesses & meningitis
57251	14	F040311	Epidural intracranial abscess	Brain abscesses & meningitis
57281	18	A022100	Salmonella meningitis	Brain abscesses & meningitis
57398	7	A133.00	Tuberculous abscess of brain	Brain abscesses & meningitis
57529	62	F040000	Cerebral intracranial abscess	Brain abscesses & meningitis
61924	21	Fyu0400	[X]Meningitis due to other specified causes	Brain abscesses & meningitis
63007	95	F00z.00	Bacterial meningitis NOS	Brain abscesses & meningitis
66107	9	F00y100	Meningitis due to bacillus pyocyaneus	Brain abscesses & meningitis
66554	2	F007z00	Unspecified meningitis in bacterial disease EC	Brain abscesses & meningitis
67432	8	F011z11	Acute aseptic meningitis	Brain abscesses & meningitis
67971	12	F040100	Cerebellar intracranial abscess	Brain abscesses & meningitis
68978	16	F00y411	Klebsiella meningitis	Brain abscesses & meningitis
69322	17	A130z00	Tuberculous meningitis NOS	Brain abscesses & meningitis
69547	3	AB65200	Cryptococcal meningitis	Brain abscesses & meningitis
72095	5	F00yz00	Other specified bacterial meningitis NOS	Brain abscesses & meningitis
73533	7	F040z00	Intracranial abscess NOS	Brain abscesses & meningitis
90288	4	F00y600	Meningitis due to pseudomonas	Brain abscesses & meningitis
95139	11	7005400	Excision of abscess of tissue of brain	Brain abscesses & meningitis
97348	6	F00y.00	Other specified bacterial meningitis	Brain abscesses & meningitis
99700	2	F007.00	Meningitis in other bacterial disease classified elsewhere	Brain abscesses & meningitis
100619	2	Fyu0300	[X]Meningitis/other specifd infectious+parasitic diseases CE	Brain abscesses & meningitis
105982	4	Fyu0000	[X]Other bacterial meningitis	Brain abscesses & meningitis
107659	1	F007700	Meningitis due to actinomycosis	Brain abscesses & meningitis
572	165955	H26..00	Pneumonia due to unspecified organism	Pneumonia
886	85086	H25..00	Bronchopneumonia due to unspecified organism	Pneumonia
1576	3842	H231.00	Pneumonia due to mycoplasma pneumoniae	Pneumonia
1849	36288	H21..00	Lobar (pneumococcal) pneumonia	Pneumonia
3683	9048	H261.00	Basal pneumonia due to unspecified organism	Pneumonia
5324	6741	H28..00	Atypical pneumonia	Pneumonia
5612	438	H224.00	Pneumonia due to staphylococcus	Pneumonia
6094	29623	H2z..00	Pneumonia or influenza NOS	Pneumonia
9043	365	H060600	Acute pneumococcal bronchitis	Pneumonia
9639	10855	H260.00	Lobar pneumonia due to unspecified organism	Pneumonia
9953	74	A116.00	Tuberculous pneumonia	Pneumonia
10086	12677	H2...00	Pneumonia and influenza	Pneumonia
11849	5155	H2y..00	Other specified pneumonia or influenza	Pneumonia
12061	660	H22y200	Pneumonia - Legionella	Pneumonia
12423	892	H223.00	Pneumonia due to streptococcus	Pneumonia
13563	1669	SP13100	Other aspiration pneumonia as a complication of care	Pneumonia
13573	570	H270000	Influenza with bronchopneumonia	Pneumonia
15912	400	H270.00	Influenza with pneumonia	Pneumonia
16287	1666	H25..11	Chest infection - unspecified bronchopneumonia	Pneumonia
19400	621	H26..11	Chest infection - pnemonia due to unspecified organism	Pneumonia

19963	982	A830.00	Q fever	Pneumonia
22009	354	A3BX400	Streptococ pneumon/cause/disease classified/oth chapters	Pneumonia
22795	484	H22..11	Chest infection - other bacterial pneumonia	Pneumonia
22835	193	H564.00	Bronchiolitis obliterans organising pneumonia	Pneumonia
23095	3015	H22z.00	Bacterial pneumonia NOS	Pneumonia
23333	912	H540000	Hypostatic pneumonia	Pneumonia
23546	241	H220.00	Pneumonia due to klebsiella pneumoniae	Pneumonia
23726	128	H24y700	Pneumonia with varicella	Pneumonia
24356	427	H540100	Hypostatic bronchopneumonia	Pneumonia
25054	495	H470312	Aspiration pneumonia due to vomit	Pneumonia
25694	1620	H23..00	Pneumonia due to other specified organisms	Pneumonia
26287	206	A3BXB00	Klebsiella pneumoniae/cause/disease classifd/oth chapters	Pneumonia
27519	157	H24y200	Pneumonia with pneumocystis carinii	Pneumonia
28634	1711	H22..00	Other bacterial pneumonia	Pneumonia
29166	87	H21..11	Chest infection - pneumococcal pneumonia	Pneumonia
29457	133	H270.11	Chest infection - influenza with pneumonia	Pneumonia
30437	112	H243.00	Pneumonia with whooping cough	Pneumonia
30591	188	H221.00	Pneumonia due to pseudomonas	Pneumonia
30653	71	H23..11	Chest infection - pneumonia organism OS	Pneumonia
31024	314	A3BXA00	Mycoplasma pneumoniae [PPLO] cause/dis classifd/oth chaptr	Pneumonia
31643	525	Q310.00	Congenital pneumonia	Pneumonia
31886	186	H060A00	Acute bronchitis due to mycoplasma pneumoniae	Pneumonia
32818	50	H510900	Pneumococcal pleurisy	Pneumonia
34251	388	H23z.00	Pneumonia due to specified organism NOS	Pneumonia
34274	54	H246.00	Pneumonia with aspergillosis	Pneumonia
35082	92	H243.11	Pneumonia with pertussis	Pneumonia
35189	74	H530300	Abscess of lung with pneumonia	Pneumonia
35745	57	H270z00	Influenza with pneumonia NOS	Pneumonia
37881	116	H222.00	Pneumonia due to haemophilus influenzae	Pneumonia
40498	110	H24..00	Pneumonia with infectious diseases EC	Pneumonia
41034	148	H240.00	Pneumonia with measles	Pneumonia
43286	11	H241.00	Pneumonia with cytomegalic inclusion disease	Pneumonia
43345	35	H511000	Pneumococcal pleurisy with effusion	Pneumonia
43884	324	H22yz00	Pneumonia due to bacteria NOS	Pneumonia
45425	2	H22y100	Pneumonia due to proteus	Pneumonia
46628	49	H501500	Pyopneumothorax	Pneumonia/Empyema
47295	9	A205.00	Pneumonic plague, unspecified	Pneumonia
48804	22	H222.11	Pneumonia due to haemophilus influenzae	Pneumonia
49398	3	H24y600	Pneumonia with typhoid fever	Pneumonia
50408	18	A730.00	Ornithosis with pneumonia	Pneumonia
50867	92	H22y.00	Pneumonia due to other specified bacteria	Pneumonia
51398	26	A3By400	Pleuropneumonia-like organism (PPLO) infection	Pneumonia
52071	10	H247000	Pneumonia with candidiasis	Pneumonia
52384	4	H22yX00	Pneumonia due to other aerobic gram-negative bacteria	Pneumonia
53753	120	Hyu0H00	[X]Other pneumonia, organism unspecified	Pneumonia
53969	2	H247z00	Pneumonia with systemic mycosis NOS	Pneumonia
60119	2	H230.00	Pneumonia due to Eaton's agent	Pneumonia
60299	8	H22y011	E.coli pneumonia	Pneumonia
60482	6	H24y300	Pneumonia with Q-fever	Pneumonia
61623	40	H24y000	Pneumonia with actinomycosis	Pneumonia

62623	9	H242.00	Pneumonia with ornithosis	Pneumonia
62632	9	H270100	Influenza with pneumonia, influenza virus identified	Pneumonia
63763	22	Hyu0A00	[X]Other bacterial pneumonia	Pneumonia
63858	26	H223000	Pneumonia due to streptococcus, group B	Pneumonia
64799	8	H571.00	Rheumatic pneumonia	Pneumonia
65419	12	H22y000	Pneumonia due to escherichia coli	Pneumonia
66362	12	H24z.00	Pneumonia with infectious diseases EC NOS	Pneumonia
67901	3	H24y100	Pneumonia with nocardiasis	Pneumonia
69782	10	H24y.00	Pneumonia with other infectious diseases EC	Pneumonia
70559	4	H24yz00	Pneumonia with other infectious diseases EC NOS	Pneumonia
70710	3	A203.00	Primary pneumonic plague	Pneumonia
72182	8	H24y400	Pneumonia with salmonellosis	Pneumonia
72193	4	F00y400	Meningitis due to klebsiella pneumoniae	Pneumonia
73735	3	H232.00	Pneumonia due to pleuropneumonia like organisms	Pneumonia
96059	54	4JUK.00	Mycoplasma pneumoniae detected	Pneumonia
96583	0	AyuKA00	[X]Klebsiella pneumoniae/cause/disease classifd/oth chapters	Pneumonia
98381	24	Hyu0B00	[X]Pneumonia due to other specified infectious organisms	Pneumonia
98782	1	H24y500	Pneumonia with toxoplasmosis	Pneumonia
101204	1871	H470.11	Aspiration pneumonia	Pneumonia
103404	1	H247100	Pneumonia with coccidioidomycosis	Pneumonia
104121	6610	H2B..00	Community acquired pneumonia	Pneumonia
106031	1	AyuK900	[X]Mycoplasma pneumoniae [PPLO]cause/dis classifd/oth chaptr	Pneumonia
106908	1	H244.00	Pneumonia with tularaemia	Pneumonia
932	797	J650.12	Empyema of gallbladder	Empyema
2375	6478	H50..00	Empyema	Empyema
6624	55	H501000	Pleural abscess	Empyema
15932	287	H501100	Thorax abscess NOS	Empyema
28228	5	F530.12	Empyema of mastoid	Empyema/Mastoiditis
34282	153	H50z.00	Empyema NOS	Empyema
34651	70	H500100	Empyema with bronchopleural fistula	Empyema
38052	26	H501300	Lung empyema NOS	Empyema
39512	57	A120100	Tuberculous empyema	Empyema
44425	133	H501200	Pleural empyema	Empyema
49452	93	H501400	Purulent pleurisy	Empyema
53494	5	H501.00	Empyema with no fistula	Empyema
59340	13	H500.00	Empyema with fistula	Empyema
59587	12	H501600	Pyothorax	Empyema
66856	0	H500000	Empyema with bronchocutaneous fistula	Empyema
99547	2	H500400	Empyema with pleural fistula NOS	Empyema
1803	517	K011.00	Nephrotic syndrome with membranous glomerulonephritis	Glomerulonephritis
2088	4490	K00..00	Acute glomerulonephritis	Glomerulonephritis
4669	196	K02y200	Chronic focal glomerulonephritis	Glomerulonephritis
5182	3314	K03z.00	Unspecified glomerulonephritis NOS	Glomerulonephritis
5417	3137	K00..11	Acute nephritis	Glomerulonephritis
7804	1967	K02..00	Chronic glomerulonephritis	Glomerulonephritis
9840	19	K010.00	Nephrotic syndrome with proliferative glomerulonephritis	Glomerulonephritis
10647	392	K02..11	Nephritis - chronic	Glomerulonephritis
10809	317	K021.00	Chronic membranous glomerulonephritis	Glomerulonephritis
11875	889	K02..12	Nephropathy - chronic	Glomerulonephritis

15097	184	K02z.00	Chronic glomerulonephritis NOS	Glomerulonephritis
17365	52	K01B.00	Nephrotic syndrome, diffuse crescentic glomerulonephritis	Glomerulonephritis
19316	155	K016.00	Nephrotic syndrome, diffuse membranous glomerulonephritis	Glomerulonephritis
20027	51	K00y000	Acute glomerulonephritis in diseases EC	Glomerulonephritis
20129	379	K00z.00	Acute glomerulonephritis NOS	Glomerulonephritis
21947	129	K017.00	Nephrotic syn difus mesangial prolifertiv glomerulonephritis	Glomerulonephritis
21989	73	K019.00	Nephrotic syn,diffuse mesangiocapillary glomerulonephritis	Glomerulonephritis
29384	123	K000.00	Acute proliferative glomerulonephritis	Glomerulonephritis
29634	180	K013.00	Nephrotic syndrome with minimal change glomerulonephritis	Glomerulonephritis
30301	40	K03X.00	Unsp nephrit synd, diff mesang prolif glomerulonephritis	Glomerulonephritis
34998	77	K020.00	Chronic proliferative glomerulonephritis	Glomerulonephritis
36125	35	K03U.00	Unspecif nephr synd, diff concentric glomerulonephritis	Glomerulonephritis
36342	94	K032y13	Mesangioproliferative glomerulonephritis NEC	Glomerulonephritis
41285	2	K0A1200	Rapid progres neph syn diffuse membranous glomerulonephritis	Glomerulonephritis
41881	247	K032y14	Mesangiocapillary glomerulonephritis NEC	Glomerulonephritis
47838	37	K00yz00	Other acute glomerulonephritis NOS	Glomerulonephritis
48261	97	K00y200	Acute focal nephritis	Glomerulonephritis
50305	11	K032y11	Hypocomplementaemic persistent glomerulonephritis NEC	Glomerulonephritis
50472	5	K018.00	Nephrotic syn,difus endocapilary proliftv glomerulonephritis	Glomerulonephritis
54312	6	K0A0500	Acute neph syn, diffuse mesangiocapillary glomerulonephritis	Glomerulonephritis
55100	26	K00y300	Acute diffuse nephritis	Glomerulonephritis
56893	11	K0A3300	Chron neph syn difus mesangial prolifrtiv glomerulonephritis	Glomerulonephritis
57168	13	K0A3200	Chron nephritic syndrom difuse membranous glomerulonephritis	Glomerulonephritis
58060	1	K0A1300	Rpd prog neph syn df mesangial prolifratv glomerulonephritis	Glomerulonephritis
60484	3	K0A2500	Recur+persist hmuria df mesangiocapilary glomerulonephritis	Glomerulonephritis
60856	4	K0A2700	Recur+persist haematuria difus crescentic glomerulonephritis	Glomerulonephritis
60857	18	K0A3700	Chronic nephritic syn diffuse crescentic glomerulonephritis	Glomerulonephritis
60960	12	K02y.00	Other chronic glomerulonephritis	Glomerulonephritis
61317	4	K0A2200	Recur+persist haematuria difus membranous glomerulonephritis	Glomerulonephritis
61494	30	K022.00	Chronic membranoproliferative glomerulonephritis	Glomerulonephritis
61814	9	K0A0700	Acute nephrotic syndrm diffuse crescentic glomerulonephritis	Glomerulonephritis
62320	10	K0A1700	Rapid progres nephritic syn df crescentic glomerulonephritis	Glomerulonephritis
62520	8	K03W.00	Unsp nephrit synd, diff endocap prolif glomerulonephritis	Glomerulonephritis
62868	3	K032300	Anaphylactoid glomerulonephritis	Glomerulonephritis
63599	41	K00y.00	Other acute glomerulonephritis	Glomerulonephritis
63615	12	K02yz00	Other chronic glomerulonephritis NOS	Glomerulonephritis

65064	4	K023.00	Chronic rapidly progressive glomerulonephritis	Glomerulonephritis
65400	5	K02y300	Chronic diffuse glomerulonephritis	Glomerulonephritis
66503	16	K0A0200	Acute nephritic syn, diffuse membranous glomerulonephritis	Glomerulonephritis
67193	29	K032y00	Nephritis unsp+OS membranoprolif glomerulonephritis lesion	Glomerulonephritis
67460	8	K001.00	Acute nephritis with lesions of necrotising glomerulitis	Glomerulonephritis
67995	9	K032000	Focal membranoproliferative glomerulonephritis	Glomerulonephritis
71709	2	Kyu0900	[X]Unsp nephrit synd, diff mesang prolif glomerulonephritis	Glomerulonephritis
73026	3	K0A3500	Chronic neph syn difus mesangiocapillary glomerulonephritis	Glomerulonephritis
94261	2	K00y100	Acute exudative nephritis	Glomerulonephritis
94350	3	K032z00	Nephritis unsp+membranoprolif glomerulonephritis lesion NOS	Glomerulonephritis
97388	1	K032y15	Mixed membranous and proliferative glomerulonephritis NEC	Glomerulonephritis
97758	2	K02y000	Chronic glomerulonephritis + diseases EC	Glomerulonephritis
99644	4	K012.00	Nephrotic syndrome+membranoproliferative glomerulonephritis	Glomerulonephritis
101358	1	K0A0400	Ac neph syn difus endocaplry prolifrative glomerulonephritis	Glomerulonephritis
105723	28	K000100	Crescentic glomerulonephritis	Glomerulonephritis
105859	8	K0A8.00	Rapidly progressive glomerulonephritis	Glomerulonephritis
107814	1	K032200	Focal glomerulon + focal recurr macroscop glomerulonephritis	Glomerulonephritis
108711	1	K000111	CGN - Crescentic glomerulonephritis	Glomerulonephritis
111029	1	K032y12	Lobular glomerulonephritis NEC	Glomerulonephritis
111751	1	K036.00	Cryoglobulinaemic glomerulonephritis	Glomerulonephritis
28084	62	A383011	lemierre's syndrome	Lemierre's
1716	3889	F55z.00	Middle ear or mastoid disorder NOS	Mastoiditis
1794	20735	7310.11	Mastoidectomy	Mastoiditis
2141	2817	7N17200	[SO]Mastoid	Mastoiditis
2351	300	7317z00	Other operation on middle ear NOS	Mastoiditis
2567	4126	F53z.00	Mastoiditis NOS	Mastoiditis
3060	466	F5z..00	Ear and mastoid disease NOS	Mastoiditis
3467	1226	7311600	Exploration of mastoid	Mastoiditis
3641	2598	7310000	Radical mastoidectomy	Mastoiditis
4738	116	7N17211	[SO]Attic of mastoid	Mastoiditis
5103	927	F55..11	Middle ear disease - other	Mastoiditis
5251	307	F531.00	Chronic mastoiditis	Mastoiditis
5625	1599	7317y00	Other specified other operation on middle ear	Mastoiditis
6539	755	7N88700	[SO]Sternomastoid	Mastoiditis
8016	1914	2D73.11	O/E - mastoid tender	Mastoiditis
9278	5137	2D9A.00	O/E -otoscopy:fluid-middle ear	Mastoiditis
9453	2942	731..11	Mastoid operations	Mastoiditis
10510	194	731..12	Middle ear operations	Mastoiditis
11221	104	F530z00	Acute mastoiditis NOS	Mastoiditis
11399	3046	F53..00	Mastoiditis and related conditions	Mastoiditis
12893	1777	7310500	Revision of mastoidectomy	Mastoiditis
13225	9552	F5...00	Diseases of the ear and mastoid process	Mastoiditis
15003	166	F531z00	Chronic mastoiditis NOS	Mastoiditis
15305	392	7H54400	Release of sternomastoid muscle	Mastoiditis
15818	212	2D73.00	O/E - pain over mastoid	Mastoiditis

16023	684	7310600	Atticoantrostomy	Mastoiditis
16200	8497	7317400	Suction clearance of middle ear	Mastoiditis
17153	67	A154.00	Tuberculous mastoiditis	Mastoiditis
17654	3265	7313.00	Drainage of middle ear	Mastoiditis
18733	153	ZF32.00	Middle ear pressure	Mastoiditis
19353	2908	731..00	Mastoid and middle ear operations	Mastoiditis
19976	238	F55yz00	Other middle ear or mastoid disorder NOS	Mastoiditis
20525	2060	7N18100	[SO]Middle ear	Mastoiditis
20842	487	7318.00	Exploration of middle ear	Mastoiditis
23507	1930	7310400	Mastoidectomy NEC	Mastoiditis
23792	2017	7311100	Atticotomy	Mastoiditis
23857	1763	7310200	Cortical mastoidectomy	Mastoiditis
23873	121	7311200	Removal or change of mastoid pack	Mastoiditis
24590	307	F522.00	Chronic suppurative otitis media, atticoantral	Mastoiditis
24733	2006	7310100	Modified radical mastoidectomy	Mastoiditis
25460	234	F55..00	Other disorders of middle ear and mastoid	Mastoiditis
25933	55	731y.00	Other specified operations on mastoid or middle ear	Mastoiditis
29184	403	7318.11	Tympanotomy and exploration of middle ear	Mastoiditis
30081	566	7317900	Excision of cholesteatoma of middle ear	Mastoiditis
30216	135	F530.11	Abscess of mastoid	Mastoiditis
32629	155	7311000	Obliteration of mastoid	Mastoiditis
34821	116	7318z00	Exploration of middle ear NOS	Mastoiditis
35246	101	7311z00	Other operation on mastoid NOS	Mastoiditis
36005	42	7318y00	Other specified exploration of middle ear	Mastoiditis
37443	656	F530.00	Acute mastoiditis	Mastoiditis
37824	61	F551.00	Adhesive middle ear disease	Mastoiditis
39333	19	7311500	Biopsy of mastoid	Mastoiditis
39796	12	7310211	Schwartze cortical mastoidectomy	Mastoiditis
39834	26	F531100	Post aural mastoid fistula	Mastoiditis
40167	67	F533.00	Postmastoidectomy complication	Mastoiditis
40680	428	731z.00	Mastoid and middle ear operations NOS	Mastoiditis
41648	115	F53y.00	Other mastoid disorders	Mastoiditis
42522	61	7313y00	Other specified drainage of middle ear	Mastoiditis
42536	167	7310300	Simple mastoidectomy	Mastoiditis
42976	131	7317.00	Other operations on middle ear	Mastoiditis
44428	29	7311700	Drainage of petrous apex of mastoid	Mastoiditis
44803	281	7311.00	Other operations on mastoid	Mastoiditis
45411	80	7311y00	Other specified other operation on mastoid	Mastoiditis
48038	334	7313z00	Drainage of middle ear NOS	Mastoiditis
48133	19	F5y..00	Other specified diseases of ear or mastoid	Mastoiditis
48314	81	F53y100	Other mastoid disorder NOS	Mastoiditis
48582	9	7310y00	Other specified exenteration of mastoid air cells	Mastoiditis
48721	53	F530000	Acute mastoiditis without complications	Mastoiditis
50034	23	F530100	Subperiosteal mastoid abscess	Mastoiditis
51376	34	F533300	Postmastoidectomy granulation cavity	Mastoiditis
52823	65	FyuP900	[X]Other perforations of tympanic membrane	Mastoiditis
53048	25	F55y.00	Other middle ear and mastoid disorders OS	Mastoiditis
53654	821	7310.00	Exenteration of mastoid air cells	Mastoiditis
53734	20	FyuP200	[X]Other chronic suppurative otitis media	Mastoiditis
55555	8	F551z00	Adhesive middle ear disease NOS	Mastoiditis
56765	840	7316.00	Plastic repair of middle ear	Mastoiditis
61856	5	7316y00	Other specified plastic repair of middle ear	Mastoiditis
62843	16	F533z00	Postmastoidectomy complication NOS	Mastoiditis
65308	14	7318000	Tympanotomy using mastoid approach	Mastoiditis

67380	7	F533000	Unspecified postmastoidectomy complication	Mastoiditis
71350	7	7310z00	Exenteration of mastoid air cells NOS	Mastoiditis
72089	22	7316z00	Plastic repair of middle ear NOS	Mastoiditis
72914	18	FyuP500	[X]Otitis media in other diseases classified elsewhere	Mastoiditis
72916	6	FyuP400	[X]Otitis media in viral diseases classified elsewhere	Mastoiditis
73271	2	FyuP800	[X]Other marginal perforations of tympanic membrane	Mastoiditis
73570	8	F530300	Acute mastoiditis with other complication	Mastoiditis
73949	3	FyuPA00	[X]Other specified disorders of tympanic membrane	Mastoiditis
83477	331	7311C00	Atticoantrostomy	Mastoiditis
94561	4	FyuP700	[X]Other mastoiditis and related conditions	Mastoiditis
96629	3	F550300	Tympanosclerosis tympanic membrane, ossicles and middle ear	Mastoiditis
97856	2	FyuU600	[X]Other disorders following mastoidectomy	Mastoiditis
98269	4	F551000	Unspecified adhesive middle ear disease	Mastoiditis
98629	2	FyuPE00	[X]Other specified disorders/middle ear+mastoid/diseases CE	Mastoiditis
98656	5	FyuP300	[X]Otitis media in bacterial diseases classified elsewhere	Mastoiditis
99403	8	FyuP000	[X]Other acute nonsuppurative otitis media	Mastoiditis
99409	4	FyuP.00	[X]Diseases of middle ear and mastoid	Mastoiditis
101916	2	FyuPC00	[X]Other specified disorders of middle ear and mastoid	Mastoiditis
102110	2	FyuP600	[X]Other specified disorders of Eustachian tube	Mastoiditis
104883	1	FyuU700	[X]Other postprocedural disorders/ear and mastoid process	Mastoiditis
106497	1	F533100	Postmastoidectomy cavity mucinous cyst	Mastoiditis
911	29010	H15..11	Quinsy	Quinsy
3605	8652	H15..00	Peritonsillar abscess - quinsy	Quinsy
6596	1410	7531100	Drainage of peritonsillar abscess	Quinsy
6971	1241	2DB5.11	O/E - quinsy present	Quinsy
7956	1471	7531111	Drainage of quinsy	Quinsy
24596	461	2DB5.00	O/E - tonsils - quinsy present	Quinsy
764	9633	G0...00	Acute rheumatic fever	Rheumatic fever
8583	357	N042000	Rheumatic carditis	Rheumatic fever
14840	5421	G0z..00	Acute rheumatic fever NOS	Rheumatic fever
15132	54	G14z.00	Rheumatic endocarditis NOS	Rheumatic fever
23619	28	G01y000	Acute rheumatic pancarditis	Rheumatic fever
24636	65	G010.00	Acute rheumatic pericarditis	Rheumatic fever
34916	4	M15y600	Erythema marginatum in acute rheumatic fever	Rheumatic fever
36886	95	G011.00	Acute rheumatic endocarditis	Rheumatic fever
44756	102	G01..00	Rheumatic fever with heart involvement	Rheumatic fever
48099	16	G012.00	Acute rheumatic myocarditis	Rheumatic fever
48189	144	G00..00	Rheumatic fever without heart involvement	Rheumatic fever
59942	19	G0y..00	Other specified acute rheumatic fever	Rheumatic fever
62404	7	G1y0.00	Rheumatic myocarditis	Rheumatic fever
68126	10	G14..00	Other chronic rheumatic endocardial disease	Rheumatic fever
68849	19	G01z.00	Acute rheumatic heart disease NOS	Rheumatic fever
73540	2	G01y.00	Other acute rheumatic heart disease	Rheumatic fever
100051	1	Gyu0000	[X]Other acute rheumatic heart disease	Rheumatic fever
101539	2	Gyu0.00	[X]Acute rheumatic fever	Rheumatic fever
105615	1	G01yz00	Other acute rheumatic heart disease NOS	Rheumatic fever
107591	15	GA0..00	Carditis due to rheumatic fever	Rheumatic fever

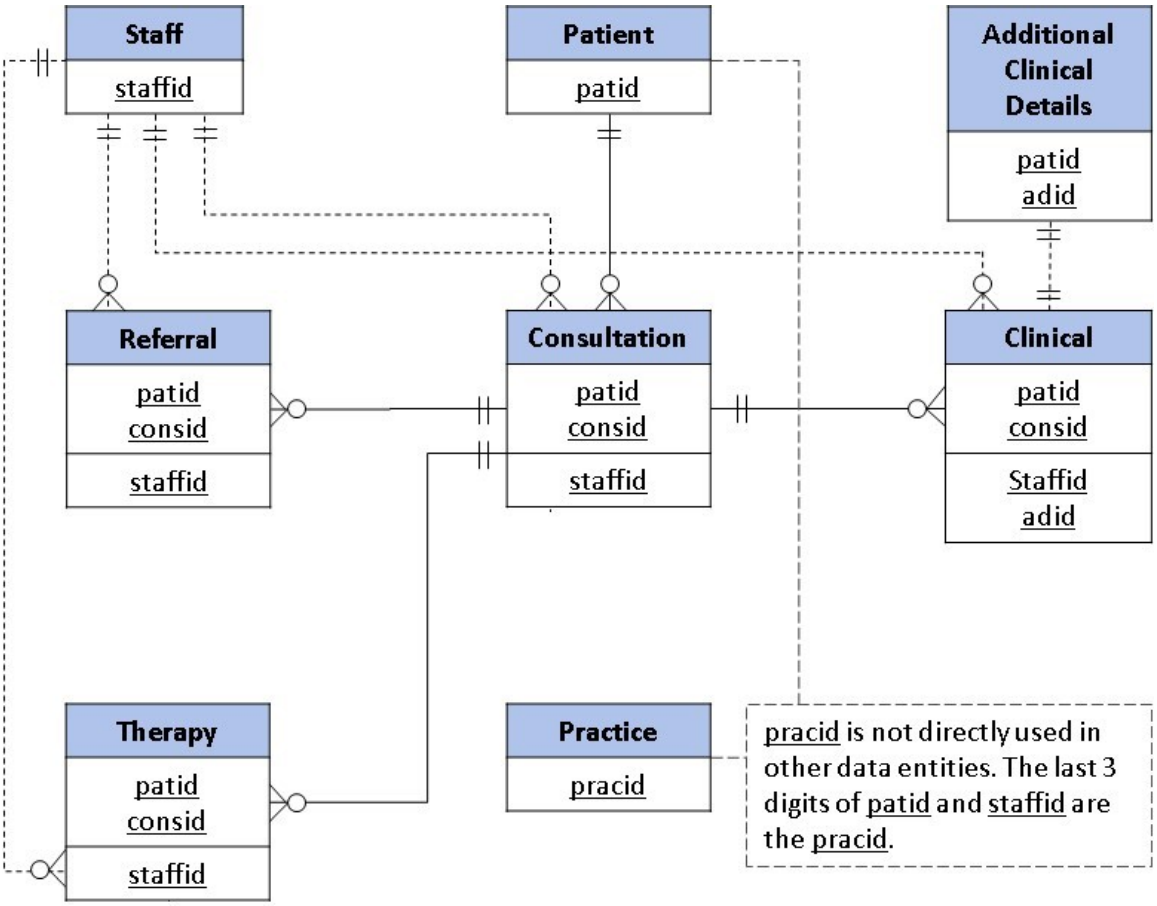
456	14945	A341.11	Scarlet fever	Scarlet fever
3218	7534	A341.12	Scarlatina	Scarlet fever
3382	12513	A3B0.00	Streptococcal infection	Scarlet fever
8210	26384	A341.00	Scarlet fever - scarlatina	Scarlet fever
16184	63	A34z.00	Streptococcal sore throat with scarlatina NOS	Scarlet fever
18469	361	A3BX100	Streptococc,gp A/cause/disease classified/to oth chapters	Scarlet fever
54777	125	A34..00	Streptococcal sore throat and scarlatina	Scarlet fever
99210	4	AyuK000	[X]Streptococc,gp A/cause/disease classified/to oth chapters	Scarlet fever
104575	160	A3B0100	Group A streptococcus infection	Scarlet fever

Complications	ICD-10 codes included	ICD-10 specific codes and terms:
Upper respiratory infections	J00, J01, J02, J03, J04, J05, J06, J31, J32, J37	J00 Acute nasopharyngitis [common cold] J01 Acute sinusitis J02 Acute pharyngitis J04 Acute laryngitis and tracheitis J05 Acute obstructive laryngitis [croup] and epiglottitis J06 Acute upper respiratory infections of multiple and unspecified sites J31 Chronic rhinitis, nasopharyngitis and pharyngitis J32 Chronic sinusitis J37 Chronic laryngitis and laryngotracheitis J03 Acute tonsillitis
lower respiratory infections	J20, J22, J40, J42	J20 Acute bronchitis J22 Unspecified acute lower respiratory infection J40 Bronchitis, not specified as acute or chronic J42 Unspecified chronic bronchitis
Otitis media	H65-H67	H65 Nonsuppurative otitis media H66 Suppurative and unspecified otitis media H67 Otitis media in diseases classified elsewhere
Mastoiditis	H68, H69, H70, H72, H73, H74, H75	H68 Eustachian salpingitis and obstruction H69 Other and unspecified disorders of Eustachian tube H70 Mastoiditis and related conditions H72 Perforation of tympanic membrane H73 Other disorders of tympanic membrane H74 Other disorders of middle ear mastoid H75 Other disorders of middle ear and mastoid in diseases classified elsewhere
Intracranial abscess	G06, G07, G08	G06 Intracranial and intraspinal abscess and granuloma G07 Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere G08 Intracranial and intraspinal phlebitis and thrombophlebitis
Peritonsillar abscess/ quinsy	J03, J35, J36, J39.0, J39.1	J35 Chronic diseases of tonsils and adenoids J36 Peritonsillar abscess J39.0 Retropharyngeal and parapharyngeal abscess J39.1 Other abscess of pharynx
Scarlet fever	A38	A38 Scarlet fever
Rheumatic fever	I00-I02	I00 Rheumatic fever without heart involvement I01 Rheumatic fever with heart involvement I02 Rheumatic chorea

Post streptococcal glomerulonephritis	N00, N01, N08	N00.0 Acute nephritic syndrome with minor glomerular abnormality N00.1 Acute nephritic syndrome with focal and segmental glomerular lesions N00.2 Acute nephritic syndrome with diffuse membranous glomerulonephritis N00.3 Acute nephritic syndrome with diffuse mesangial proliferative glomerulonephritis N00.4 Acute nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis N00.5 Acute nephritic syndrome with diffuse mesangiocapillary glomerulonephritis N00.6 Acute nephritic syndrome with dense deposit disease N00.7 Acute nephritic syndrome with diffuse crescentic glomerulonephritis N00.8 Acute nephritic syndrome with other morphologic changes N00.9 Acute nephritic syndrome with unspecified morphologic changes N01 Rapidly progressive nephritic syndrome N08 Glomerular disorders in diseases classified elsewhere
Pneumonia	J13, J15-J17, J18	J13 Pneumonia due to Streptococcus pneumoniae J15 Bacterial pneumonia, not elsewhere classified J16 Pneumonia due to other infectious organisms, not elsewhere classified J17 Pneumonia in diseases classified elsewhere J18 Pneumonia, unspecified organism
Pleurisy	J90, J94.8, J94.9	J90 Pleural effusion, not elsewhere classified J94.8 Other specified pleural conditions J94.9 Pleural condition, unspecified
Empyema	J85, J86	J85 Abscess of lung and mediastinum J86 Pyothorax
Meningitis	A39, G00, G01, G03	A39 Meningococcal infection G00 Bacterial meningitis, not elsewhere classified G01 Meningitis in bacterial diseases classified elsewhere G03 Meningitis due to other and unspecified causes

Bloodstream infections (Septicaemia/ Sepsis/ bacteraemia)	A40, A41.0, A41.1, A41.2, A41.4, A41.5, A41.8, A41.9, A42.7, A49, R65.2, B95, B96, B99	A40 Streptococcal sepsis A41.0 Sepsis due to Staphylococcus aureus A41.1 Sepsis due to other specified staphylococcus A41.2 Sepsis due to unspecified staphylococcus A41.4 Sepsis due to anaerobes A41.5 Sepsis due to other Gram-negative organisms A41.8 Other specified sepsis A41.9 Sepsis, unspecified organism A42.7 Actinomycotic sepsis A49 Bacterial infection of unspecified site R65.2 Severe sepsis B95 Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere B96 Other bacterial agents as the cause of diseases classified elsewhere B99 Other and unspecified infectious diseases
Symptoms and signs involving the circulatory and respiratory systems	R00-R99	R00-R09 Symptoms and signs involving the circulatory and respiratory systems R10-R19 Symptoms and signs involving the digestive system and abdomen R20-R23 Symptoms and signs involving the skin and subcutaneous tissue R25-R29 Symptoms and signs involving the nervous and musculoskeletal systems R30-R39 Symptoms and signs involving the genitourinary system R40-R46 Symptoms and signs involving cognition, perception, emotional state and behavior R47-R49 Symptoms and signs involving speech and voice R50-R69 General symptoms and signs R70-R79 Abnormal findings on examination of blood, without diagnosis R80-R82 Abnormal findings on examination of urine, without diagnosis R83-R89 Abnormal findings on examination of other body fluids, substances and tissues, without diagnosis R90-R94 Abnormal findings on diagnostic imaging and in function studies, without diagnosis R97-R97 Abnormal tumor markers R99-R99 Ill-defined and unknown cause of mortality

Appendix 21. An entity relationship diagram between the CPRD tables used, depicting how linkage was completed (Chapter 3, Page 1 of 2)



The CPRD Tables and the linking process depicted above are further explained in the following:

CPRD Data table	Description	Linkage
Patient	Contains patient demographics and patient registration details.	Links to all tables (apart from the Staff table) using [patid], a unique CPRD patient ID. Linked to the consultation table for this research.
Practice	Contains details of CPRD included practices, the regions and data collection quality markers of those practices.	The last three digits of [patid] provides the GP practice ID and was used to link to the Practice table in this way.
Staff	Contains a record and details for each member of the practice staff.	Links with the Consultation using [staffid], a unique staff ID.
Consultation	Includes information on the type of consultation as entered by the GP.	Links to the events that occur as part of the consultation via consid (unique consultation ID). Link to the Clinical, Referral

		and Therapy tables using [patid] and [consid].
Clinical	Contains all the medical history data entered, including symptoms, signs and diagnoses. Data is coded using Read codes.	Table contains [patid], [consid], and [staffid], to link to tables. Consultation table was linked in this way. An Additional clinical details table was also linked to using [patid] and [adid] (a unique additional clinical ID variable).
Additional Clinical	Contains additional medical history data for a clinical event.	Linked to the Clinical table using (described above).
Referral	Contains information on patient referrals to external care centres (e.g. to hospitals for inpatient or outpatient care), also includes specialty and referral type.	Contains [patid], [consid] to link to the Consultation table. (Can also be linked to the Staff table using [staffid].)
Therapy	Contains details of all prescriptions issued by the GP. Drug products are recorded by the GP using the Gemscript product code system.	Linked to the Consultation table using [patid] and [consid]. Can also be linked to the Staff table using [staffid].

Appendix 22. Variables retained from the linked CPRD Gold extract tables (Chapter 3, Page 1 of 6)

	Variable name	Description	Data type	Format: Maximum string length	Table originates from	Linkage and data management notes
1	patid	Encrypted unique identifier given to a patient in CPRD	Integer	20	-Patient -Consultation -Clinical -Additional Clinical Details -Referral -Therapy	Unique ID used to link with all tables (apart from the Staff table). The last 3 digits provides the GP Practice ID and was used to link to the Practice table in this way.
2	gender	Patient's gender	Integer	1	Patient	
3	yob	Patient's year of birth	Integer	4	Patient	
4	mob	Patient's month of birth (for those aged under 16). 0 indicates no month set	Integer	2	Patient	
5	prescr	Type of prescribing exemption the patient has currently (e.g. medical or maternity)	Integer	3	Patient	
6	frd	Date the patient first registered with the practice. If patient only has 'temporary' records, the date is the first encounter with the practice; if patient has 'permanent' records it is the date of the first 'permanent' record (excluding preceding temporary records)	Date	dd/mm/yyyy	Patient	
7	crd	Date the patient's current period of registration with the practice began (date of the first 'permanent' record after the latest transferred out period). If there are no 'transferred out periods' the date is equal to [frd]	Date	dd/mm/yyyy	Patient	
8	regstat	Status of registration detailing gaps and temporary patients	Integer	2	Patient	
9	reggap	Number of days missing in the patient's registration details	Integer	5	Patient	
10	tod	Date the patient transferred out of the practice, if relevant. Empty for patients who have not transferred out	Date	dd/mm/yyyy	Patient	

	Variable name	Description	Data type	Format: Maximum string length	Table originates from	Linkage and data management notes
11	toreason	Reason the patient transferred out of the practice includes 'Death' as an option	Integer	3	Patient	
12	deathdate	Date of death of patient, derived using CPRD Gold algorithm	Date	dd/mm/yyyy	Patient	
13	accept	Flag to indicate whether the patient has met certain quality standards (1: acceptable, 0: unacceptable)	Integer	1	Patient	Used alongside [uts] to retain quality records
14	pracid	Encrypted unique identifier given to specific practice in CPRD	Integer	3	Practice	The last three digits of [patid] and [staffid] are the [pracid]; deriving a variable using the Patient table [patid] variable permitted linkage to this Practice table
15	region	Value to indicate where in the UK the practice is based. The region denotes the Strategic Health Authority for practices within England, and the country i.e. Wales, Scotland, and Northern Ireland	Integer	3	Practice	
16	lcd	Date of the last collection for the practice	Date	dd/mm/yyyy	Practice	
17	uts	Date at which the practice data is deemed to be of research quality. Derived using a CPRD Gold algorithm that primarily looks at practice death recording and gaps in data	Date	dd/mm/yyyy	Practice	Used alongside [accept] to retain quality records
18	staffid	Encrypted unique identifier given to the practice staff member entering the data	Integer	20	-Staff -Consultation -(Clinical)	Links with the Consultation table using this unique field. (A value of 0 indicates that the staffid is unknown in the Consultation file)
19	StaffGender	Staff's gender	Integer	1	Staff	Original variable name [gender], altered when linking with Patient table so as not to confuse with patient gender

	Variable name	Description	Data type	Format: Maximum string length	Table originates from	Linkage and data management notes
20	role	Role of the member of staff who created the event	Integer	3	Staff	
21	ConsEventdate	Date associated with the event, as entered by the GP	Date	dd/mm/yyyy	Consultation	Original variable name [eventdate], altered to distinguish from event dates in other tables.
22	sysdate	Date the event was entered into Vision	Date	dd/mm/yyyy	Consultation	
23	constype	Type of consultation (e.g. Surgery consultation, night visit, emergency)	Integer	3	Consultation	
24	consid	The consultation identifier linking events at the same consultation, when used in combination with pracid	Integer	20	-Consultation -Clinical -Referral -Therapy	Used to link to clinical table alongside [patid]
25	ClinicalEventdate	Date associated with the event, as entered by the GP	Date	dd/mm/yyyy	Clinical	Original variable name [eventdate], altered to distinguish from event dates in other tables.
26	Clinicalsysdate	Date the event was entered into Vision	Date	dd/mm/yyyy	Clinical	Original variable name [sysdate], altered to distinguish from dates in other tables.
27	ClinicalConstype	Code for the category of event recorded within the GP system (e.g. diagnosis or symptom)	Integer	3	Clinical	Original variable name [constype]
28	medcode	CPRD unique code for the medical term selected by the GP	Integer	20	Clinical	Read codes utilised to find related medcodes to identify the initial patient cohort (uncomplicated RTIs) and complications (more severe infections)
29	adid	Identifier that allows additional information to be retrieved for this event, when used in combination with pracid. A value of 0 signifies that there is no additional information associated with the event	Integer	20	Clinical	

	Variable name	Description	Data type	Format: Maximum string length	Table originates from	Linkage and data management notes
30	enttype	identifier that represents the structured data area in Vision where the data is entered	Integer	5	Additional Clinical Details	
31	adid	Identifier that allows information about the original clinical event to be retrieved, when used in combination with pracid	Integer	20	Additional Clinical Details	
32	data1	Depends on entity type	Numeric date	15.3 dd/mm/yy	Additional Clinical Details	
33	data2	Depends on entity type	Numeric date	15.3 dd/mm/yy	Additional Clinical Details	
34	data3	Depends on entity type	Numeric date	15.3 dd/mm/yy	Additional Clinical Details	
35	data4	Depends on entity type	Numeric date	12 dd/mm/yy	Additional Clinical Details	
36	data5	Depends on entity type	Numeric date	12 dd/mm/yy	Additional Clinical Details	
37	data6	Depends on entity type	Numeric date	12 dd/mm/yy	Additional Clinical Details	
38	data7	Depends on entity type	smallint	4 dd/mm/yy	Additional Clinical Details	
39	RefEventDate	Date associated with the event, as entered by the GP	Date	dd/mm/yyyy	Referral	Original variable name [eventdate], altered to distinguish from event dates in other tables.
40	Refconstype	Code for the category of event recorded within the GP system (e.g. management or administration)	Integer	3	Referral	Original variable name [constype], altered to distinguish from the same variable name in other tables.
41	Refconsid	Identifier that allows information about the consultation to be retrieved, when used in combination with pracid	Integer	20	Referral	Original variable name [consid], altered to distinguish from the same variable name in other tables.
42	Refmedcode	CPRD unique code for the medical term selected by the GP	Integer	20	Referral	Original variable name [medcode], altered to distinguish from the same variable name in other tables.

	Variable name	Description	Data type	Format: Maximum string length	Table originates from	Linkage and data management notes
43	Refstaffid	Identifier of the practice staff member entering the data. A value of 0 indicates that the staffid is unknown	Integer	20	Referral	Original variable name [staffid], altered to distinguish from the same variable name in other tables.
44	Refsource	Classification of the source of the referral e.g. GP, Self	Integer	20	Referral	
45	inpatient	Classification of the type of referral, e.g. Day case, In patient	Integer	2	Referral	
46	attendance	Category describing whether the referral event is the first visit, a follow-up etc.	Integer	2	Referral	
47	urgency	Classification of the urgency of the referral e.g. Routine, Urgent	Integer	2	Referral	
48	TherapyEventdate	Date associated with the event, as entered by the GP	Date	dd/mm/yyyy	Therapy	Original variable name [eventdate], altered to distinguish from the same variable name in other tables.
49	prodcode	CPRD unique code for the treatment selected by the GP	Integer	20	Therapy	
50	TherapyTextid	Identifier that allows freetext information (dosage) on the event to be retrieved, when used in combination with [pracid] and [eventtype]:"Therapy". A value of 0 indicates that there is no freetext information for the event. Use the Common Dosages Lookup (constituting ~95% of dosage strings in data) to interpret values <100,000	Character	50	Therapy	
51	bnfcode	Code representing the chapter and section from the British National Formulary for the product selected by the GP	Integer	5	Therapy	
52	qty	Total quantity entered by the GP for the prescribed product	Integer	20	Therapy	

	Variable name	Description	Data type	Format: Maximum string length	Table originates from	Linkage and data management notes
53	ndd	Numeric daily dose prescribed for the event. Derived using a CPRD algorithm on common dosage strings (represented by textid <100,000). Value is set to 0 for all dosage strings represented by a non-numeric textid	Character	14	Therapy	
54	numdays	Number of treatment days prescribed for a specific therapy event	Integer	20	Therapy	
55	numpacks	Number of individual product packs prescribed for a specific therapy event	Integer	8	Therapy	
56	packtype	Pack size or type of the prescribed product	Integer	10	Therapy	
57	issueseq	Number to indicate whether the event is associated with a repeat schedule. Value of 0 implies the event is not part of a repeat prescription. A value of =>1 denotes the issue number for the prescription within a repeat schedule	Integer	20	Therapy	

Appendix 23. CPRD data flow and management of patient records (Chapter 3, Page 1 of 1)

		Patients	Consultations
Extract (pts with an RTI medcode consultation within study period (01/04/2010- 31/03/2017)		**3,416,265**	**17,823,685**
# Excluded: Not up to standard (UTS) practices at the date of consultation		23	278,425
# Excluded: Temporary patient		9	82,397
# Excluding outside of study period (i.e. >31/03/2017)		22	27,071
Sub-total		**3,416,211**	**17,435,792**
De-duplicates			
	# Duplicate consultations with all the same variables	0	410,137
	# Duplicate consultations, variation in BNF code for non-antibiotic drugs (i.e. other drugs prescribed, maybe multiple, retained 1 per cons)	0	31,892
	# Duplicate consultations, variation in antibiotic quantity (dropped the record with lower quantity)	0	2,379
	# Duplicate consultations where other prescriptions given, kept record with antibiotic	0	4,807,002
	# Duplicate consultations with variation in [issueseq], dropped duplicate	0	1,251
	# duplicate consultations due to duplicate entry of [prodcode]	0	2,860
# Excluded: Clinical date mismatch with consultation date. [generated a 60 day buffer (before and after) between clinical and consultation date. Assuming those outside of 60 days are usually transfers or errors (not including where clinical dates are blank)]		1,864	305,053
De-duplicates 2			
	# Duplicate consultations with more than 1 prescription, not antibiotic related, kept one record	0	107,479
	# Duplicate consultation with different [medcode] within the same RTI infection group, retain the record with antibiotic prescription, if prescribed	0	63,545
	# Duplicate consultation with different [medcode] within the same RTI infection group, and duplicate for antibiotic too, have retained the duplicate with antibiotic with longer antibiotic duration	0	41,736
	# Duplicate consultation with nonsensical data: variations in gender or DOB/age (dropped all)	9	90
	# Duplicate consultations with the same RTI group, but multiple antibiotics prescribed/rows, retaining 1	0	36,648
# Exclude duplicate due to error in [consid], based on [patid] and [consultation event date] (same patient, same day consultation, different consultation id)		0	145,833
For total RTI consultations, # excluded duplicates due to RTI group duplicates (i.e. record for lower RTI and sore throat symptom imputed for same consultation)		0	264,870
# Excluded non-England		883,836	3,151,206
Total: Included in initial analysis, including FY 2010/11		**2,530,502**	**8,063,811**
Changing study duration to 01/04/2011-31/03/2017, (dropping FY=2010/11)		331,900	1,583,011
Total: Included in analysis		**2,198,602**	**6,480,800**

Appendix 24. CPRD patient record eight step deterministic linkage algorithm and proportion of records matched at each step (- the 5 first steps which use NHS number are retained) (Chapter 3, Page 1 of 1)

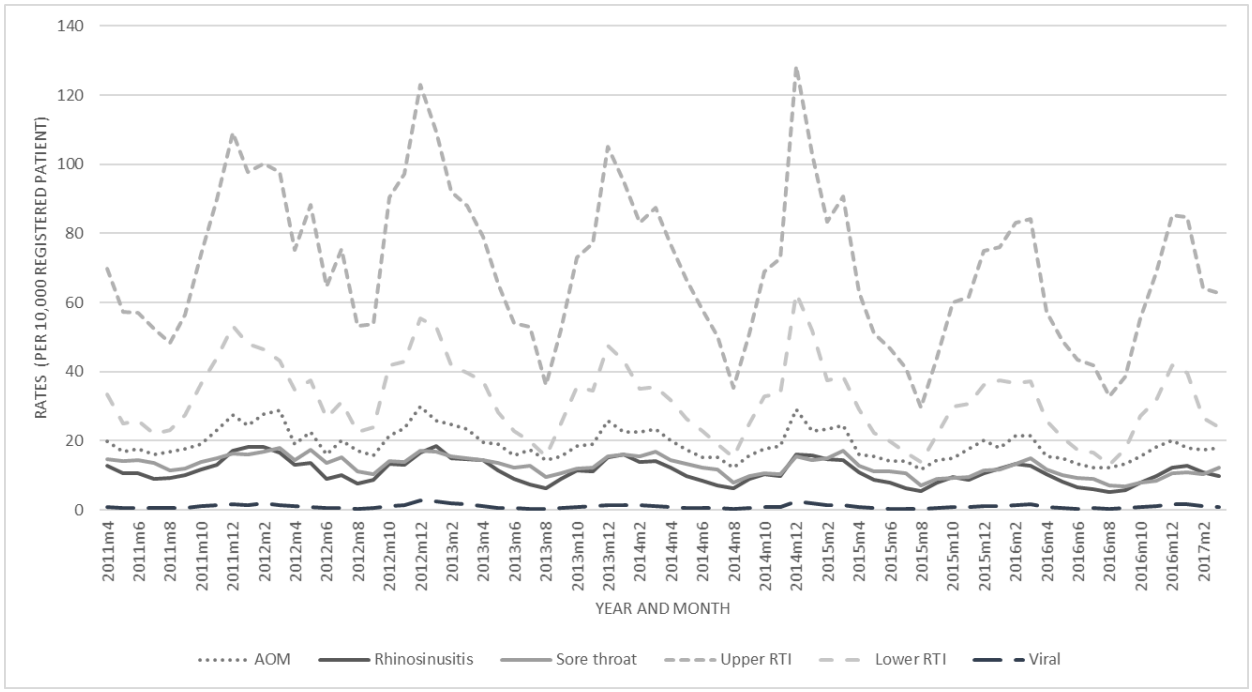
Step	Matched	HES Matched (%)	ONS Matched (%)
1	Exact NHS number, sex, date of birth, postcode	67.19	60.29
2	Exact NHS number, sex, date of birth	29.05	35.11
3	Exact NHS number, sex, postcode, partial date of birth	0.18	1.45
4	Exact NHS number, sex, partial date of birth	0.23	1.28
5	Exact NHS number, postcode	0.05	0.21
6	Exact sex, date of birth and postcode (where NHS number does not contradict the match, the date of birth is not the 1st of January and the postcode not on the communal establishment list)	3.06	1.26
7	Exact sex, date of birth and postcode (where the NHS number does not contradict the match and the date of birth is not the 1st of January)	0.18	0.23
8	Exact NHS number	0.07	0.17

Source: CPRD linkage documents

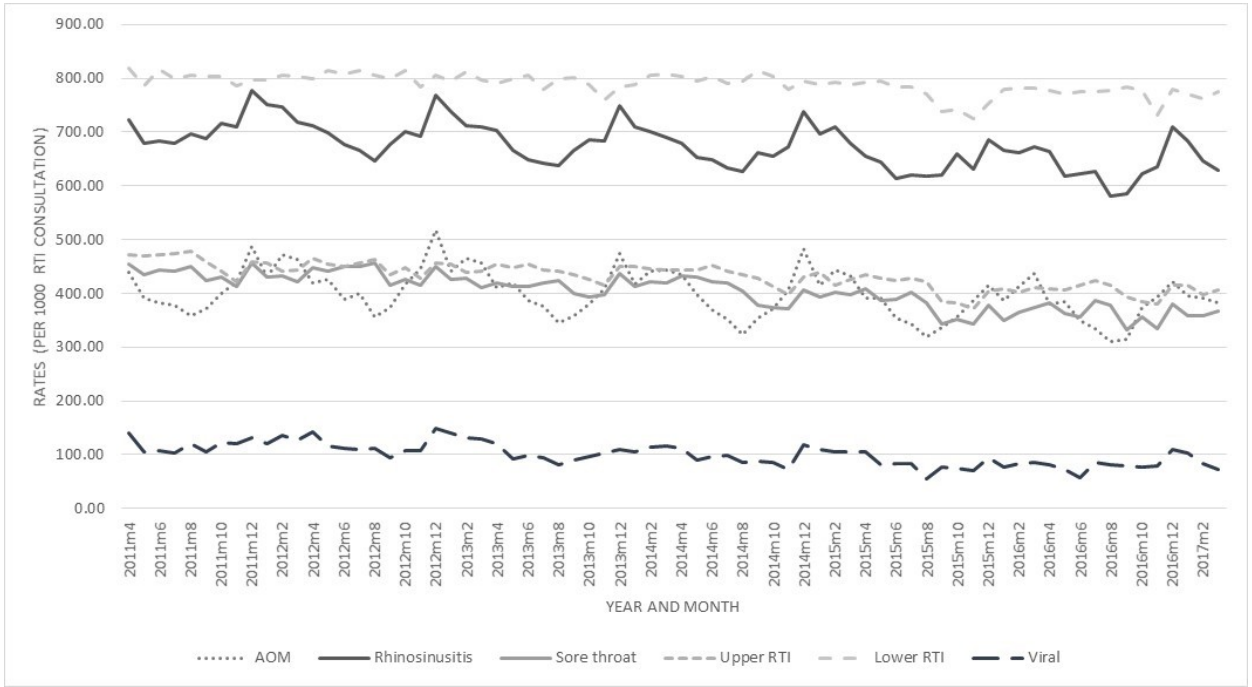
The sequential matching steps undertaken (i.e. if the CPRD patient record was matched in the first step, it was no longer available for matching in the subsequent steps) were based on the following variables: NHS number (which uniquely identifies all patients in England), date of birth, sex and postcode. Records which matched on steps 1-5 were retained and returned by CPRD as the successfully linked patients in two separate HES and ONS files. Matching on steps 1-5 represent the vast majority of records and are considered to be the more definitive matches. Where patients linked to multiple records, e.g. multiple death records, these were removed prior to receiving the returned files.

Appendix 25. Time series of antibiotic prescribing by different diagnostic groups consulted (Chapter 4, Page 1 of 1)

A) Depicts antibiotic prescribing rate by registered patients (per 10,000 registered patient)

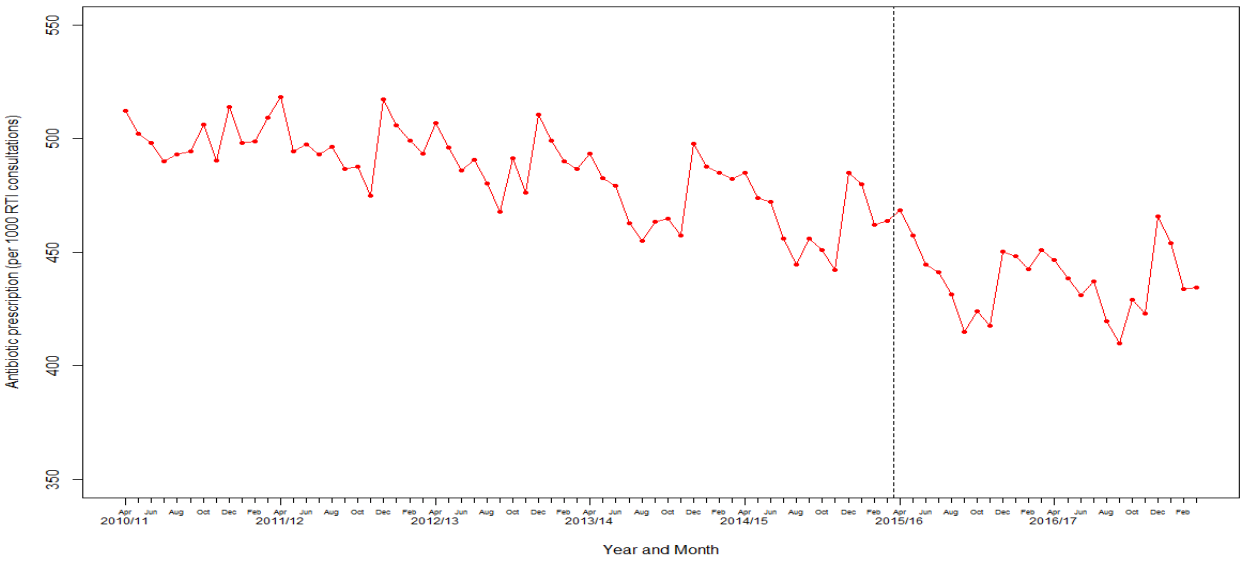


B) Depicts antibiotic prescribing rate by consultation (per 1,000 RTI consultation)



The below provides a summary pre-analysis of the data and a figure to visualise the monthly England total antibiotic prescribing trend for RTI consultations.

England, April 2010 - March 2017 (RTI)			
	England rate (per 1000 consultation)	Pre-QP rate	Post-QP rate
Min.	409.8	442.3	409.8
1st Qu.	446.2	467.1	427.7
Median	468.2	485.0	437.8
Mean	467.3	481.9	438.1
3rd Qu.	488.4	493.7	448.7
Max.	518.3	518.3	468.5



The preliminary OLS (ordinary least squares) regression results, seen in the table below, suggest that the estimate of the intercept was 527.16. The existing trend was decreasing over time by 0.93 per 1,000 RTI consultations, this value was statistically significant (p<0.0001). The initial regression model also suggests that there was a drop in antibiotic prescribing of 14.83 per 1,000 RTI consultation per month (highly statistically significant p<0.0001). There was also a trend increase of 0.36 per 1000 RTI consultations, however this was not statistically differentiable from zero. Based on these preliminary results, the intervention led to a level decrease in antibiotic prescribing. The trend increase could have been due to seasonality and hence was subsequently adjusted in the final model for this data.

Coefficients:	Estimate	Standard Error	t-value	p-value
(Intercept)	527.16257	3.17834	165.861	<0.0001
time	-0.92828	0.06737	-13.778	<0.0001
level	-14.82705	3.37974	-4.387	<0.0001
trend	0.35966	0.20225	1.778	0.0807

Seasonality as well as the trend (and related white noise) are the components that determine the choice and order of model, with adjustments made to the autoregressive (AR) operator and the moving average (MA) operator of the generalised linear square (GLS) model. Several tools were used to identify the order of the AR and MA parameters to be used and to then assess the fit of the finalised GLS model (See Chapter 3 for further detail):

- Durbin-Watson test
- Standardised residuals
- The autocorrelation (ACF) and partial autocorrelation (PACF) functions
- Likelihood ratio test and the Akaike Information Criterion (AIC) were used to select the model with the fewer parameters that fit the model best, this is often used as a diagnostic test to compare different model fits and validate the estimated preferential model parameters to use
- Q-Q plots of standard residuals

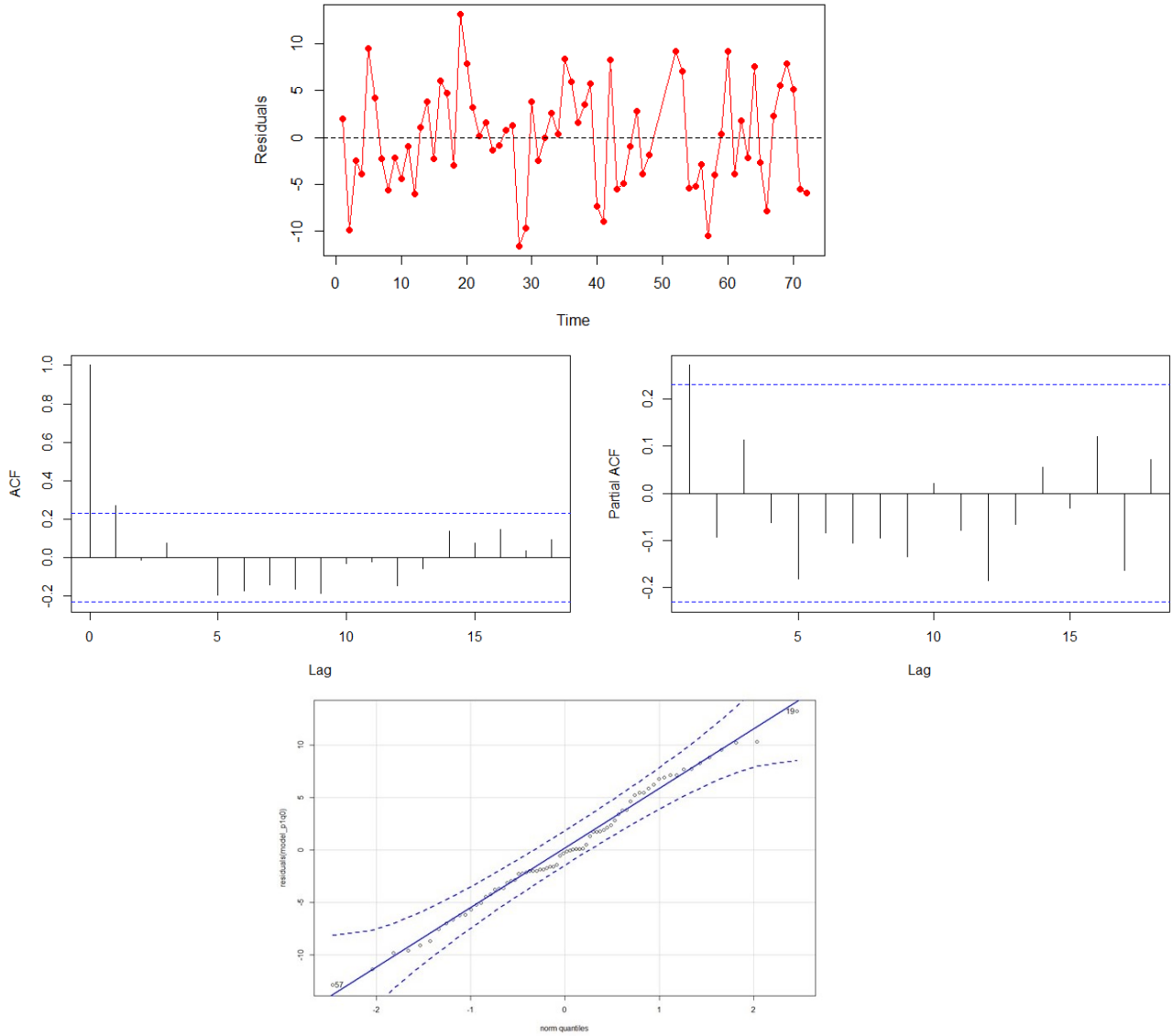
The below outline the results from these tools.

Identifying model order and diagnostic tests of fit:

Durbin-Watson test (DWT):

Lag	Autocorrelation	D-W Statistic	p-value
1	0.398597763	1.168880	<0.0001
2	0.024328119	1.895133	0.558
3	0.004662815	1.896872	0.690
4	-0.021594769	1.888456	0.690
5	-0.091888880	2.019864	0.716
6	-0.088611879	2.002529	0.684
7	-0.097555722	1.973062	0.682
8	-0.088334972	1.947930	0.690
9	-0.025511204	1.779096	0.878
10	0.135445620	1.383354	0.062
11	0.098124317	1.446667	0.164
12	-0.041470035	1.715183	0.138
Alternative hypothesis: rho[lag] != 0			

Plots of a) residuals over time b) Autocorrelation function (ACF) and c) Partial ACF (PACF) prior to applying an ARMA model, and d) quintile-quintile plot (Q-Q plot) of AR(1)MA(0) model.



The DWT function computes bootstrapped *p*-values for the Durbin-Watson statistics. The findings suggest Lag 1 is highly statistically significant (autocorrelation is closest to two at this lag).

The plot of residuals exhibits no real pattern, and that the residuals are most probably observations of white noise sequence.

The autocorrelated functions display exponential decay in the ACF plot; as the lags gets further apart, the degree of relationship becomes smaller and smaller. There is potnetialy a significant lag or spike at point 1 in the PACF and perhaps at point 1 in the ACF plot (the ACF spike (MA1) was assessed as a comparator model seperately). AR(1)MA(0) model was chosen following assessment using Likelihood ratio test, Akaike Information Criterion, and q-q plot of different model fits.

Running the final model, Correlation structure AR(1)MA(0):

Coefficients:	Value	Standard Error	t-value	p-value
(Intercept)	527.5621	3.539929	149.03182	0.0000
time	-0.945	0.087688	-10.77636	0.0000
level	-13.1403	4.248553	-3.09289	0.0031
trend	0.2973	0.26015	1.14289	0.2579
AIC	481.3206	LogLik: -223.6603		
BIC	520.0239	Phi: 0.2804493		

The model fit can be seen using the AIC (Akaike Information Criterion) of 481.32 and the BIC (Bayesian Information Criterion) of 520.0.02. These were compared to other model fit outputs for models which were ran, for example seasonality adjusted AR(1)MA(1) (results for LRT test for these models can be seen below).

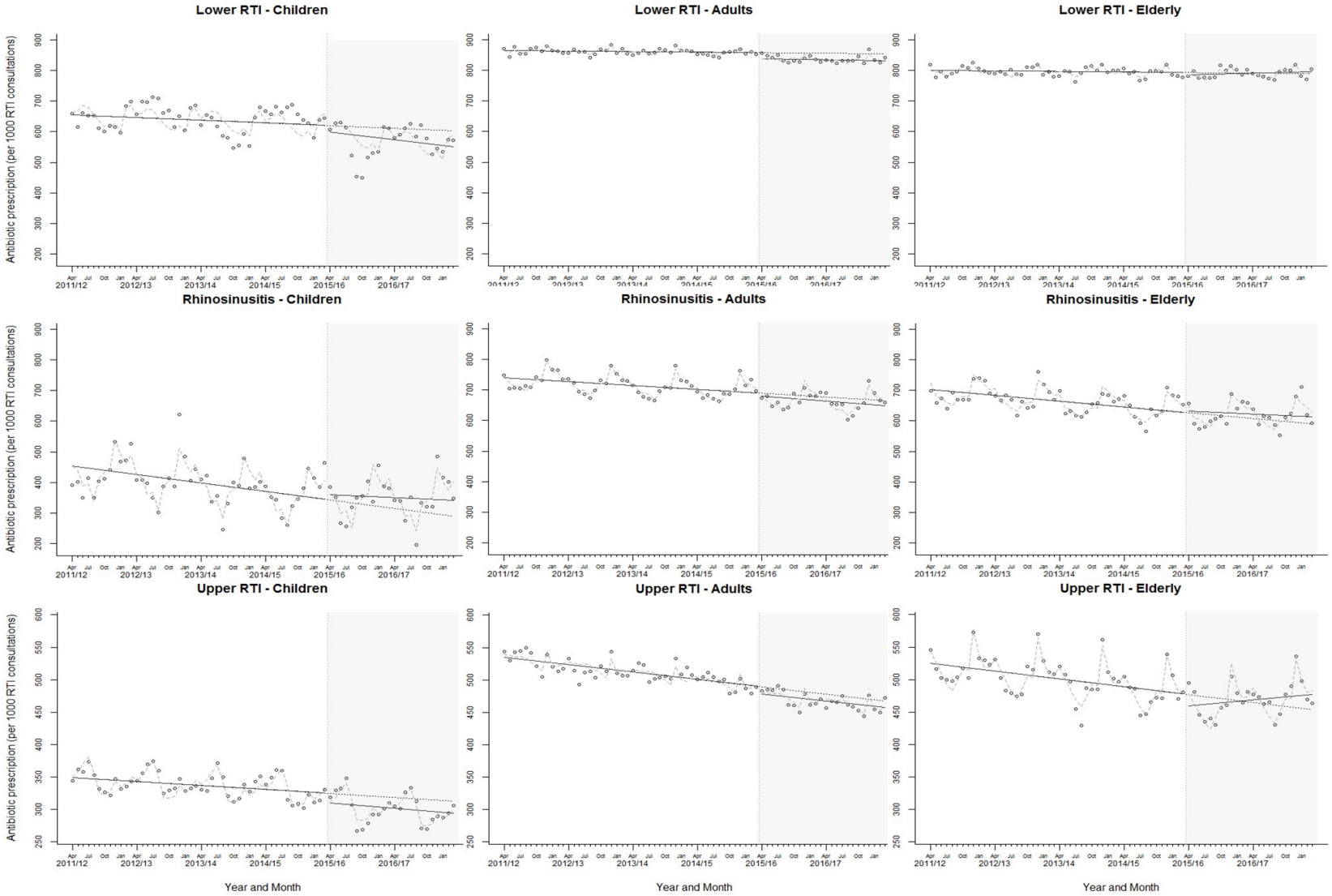
The resultant coefficients from the final model shows that the estimated intercept was 527.56 per 1,000 RTI consultations. The intercept term denotes the pre-existing level at time zero. The time coefficient indicates the existing trend pre-QP, this showed a statistically significant decrease in the pre-QP trend of 0.95 prescriptions per 1000 RTI consultations on average per month. At the time the QP was introduced there was a level drop of 13.14 antibiotic prescriptions per 1,000 RTI consultations (p<0.05), with the trend post-QP increasing slightly by 0.3 antibiotic prescriptions per 1,000 RTI consultations, although his was not a statistically significant estimate (p=0.2579).

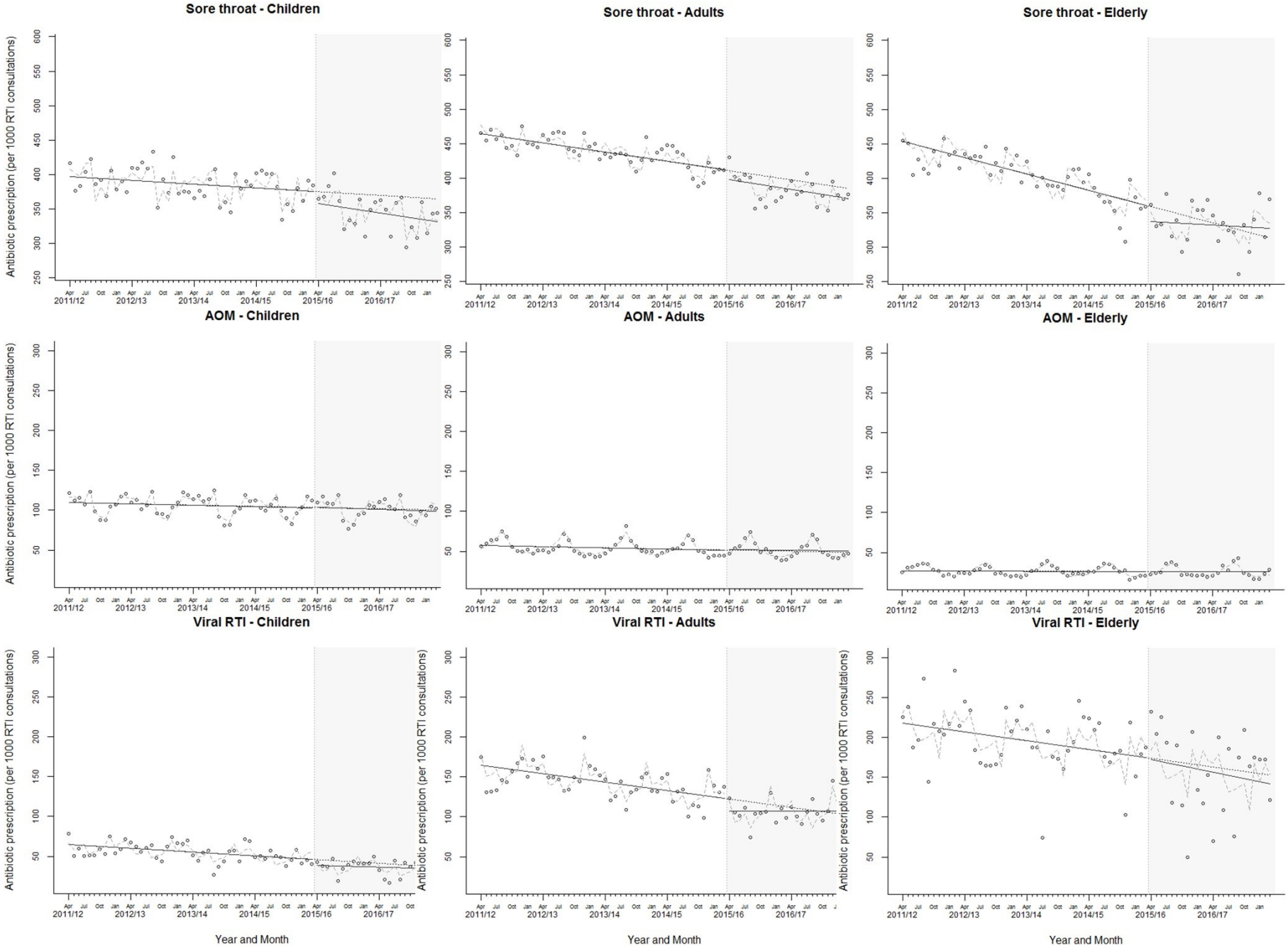
LRT diagnostic test, comparing AR(1)MA(0) to AR(1)MA(1):

	Model	df	AIC	BIC	logLik	Test	L.Ratio	p-value
model_p1q1	1	18	482.2733	523.2533	-223.1367			
model_p1q0	2	17	481.3206	520.0239	-223.6603	1 vs 2	1.047244	0.3061

The above LRT results suggest that unable to reject that these two models are the same (p=0.3061), i.e. adding an MA would not improve the model fit, furthermore the AIC and BIC values are smaller for the AR(1)MA(0) model and confirms that this model was the better fit. Q-Q plots of both models were also assessed. A well-fitting Q-Q plot of the residuals can be seen above for AR(1)MA(0).

Appendix 27. Time series analysis of antibiotic prescribing for RTI consultations by different infection groups and age, in England from April 2011 to March 2017 (Chapter 4, Page 1 of 1)




Sore throat - Children
Sore throat - Adults
Sore throat - Elderly
AOM - Children
AOM - Adults
AOM - Elderly
Viral RTI - Children
Viral RTI - Adults
Viral RTI - Elderly
Antibiotic prescription (per 1000 RTI consultations)
Year and Month
2011/12
2012/13
2013/14
2014/15
2015/16
2016/17

Appendix 28. Related findings from the ITS analysis on the change in trend and level of antibiotic prescribing for RTIs and the relative and absolute changes post-QP, by infection group and age (Chapter 4, Page 1 of 2)

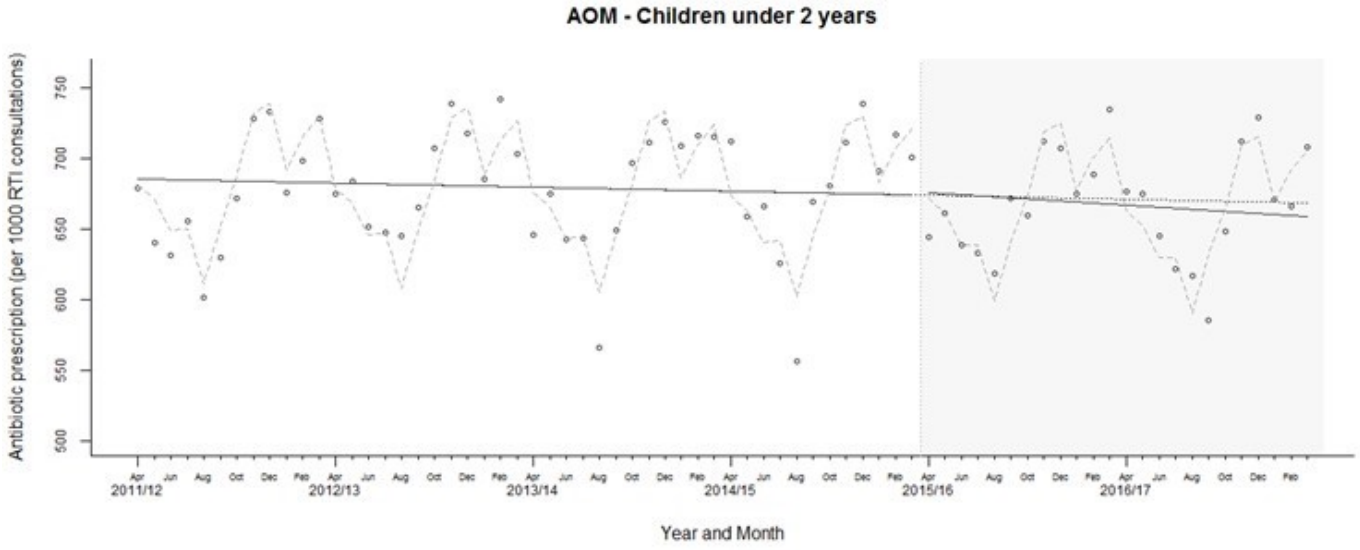
RTI group		Estimate of intercept	Pre-QP trend (*p*-value)	Change in level (*p*-value)	Change in post-QP trend (*p*-value)	Absolute change post 12 months	Relative change (%) post 12 months	Absolute change post 24 months	Relative change (%) post 24 months
Acute Otitis Media	Total	65.80 (0.0000)	-0.11 (0.0126)	-0.36 (0.8603)	-0.02 (0.8827)	0.58	0.9	0.81	1.3
	Children	116.87 (0.0000)	-0.13 (0.0794)	-0.38 (0.9137)	-0.08 (0.7215)	-0.56	-0.51	-1.50	-1.4
	Children<2	682.04 (<0.0001)	-0.23 (<0.0000)	2.25 (0.4393)	-0.53 (0.0122)	-4.08	-0.57	-10.41	-1.4
	Children 2-4	631.63 (<0.0001)	-0.65 (0.0031)	-5.45 (0.6007)	-0.76 (0.2349)	-14.60	-2.37	-23.74	-3.9
	Children 5-15	532.75 (<0.0000)	-1.06 (0.0004)	-17.24 (0.1834)	-0.45 (0.5845)	-22.62	-4.6	-28.0	-5.8
	Adult	52.89 (0.0000)	-0.12 (0.0586)	0.87 (0.7459)	0.05 (0.7875)	1.44	3.3	2.01	4.8
	Elderly	23.58 (0.0000)	-0.01 (0.6168)	-0.51 (0.7532)	0.03 (0.7547)	-0.15	-0.7	0.22	1.0
Rhinosinusitis	Total	729.26 (0.0000)	-0.62 (0.0002)	-12.71 (0.0553)	-0.47 (0.3091)	-6.36	-1.0	-5.91	-0.9
	Children	455.68 (0.0000)	-2.30 (0.0000)	16.61 (0.0862)	1.47 (0.0162)	34.27	9.1	51.92	14.8
	Adult	745.57 (0.0000)	-1.05 (0.0000)	-9.35 (0.0470)	-0.287 (0.2993)	-12.80	-1.9	-16.24	-2.4
	Elderly	724.19 (0.0000)	-1.56 (0.0000)	3.79 (0.1265)	0.73 (0.0001)	12.57	2.0	21.36	3.5
Sore throat	Total	462.08 (0.0000)	-1.04 (0.0000)	-13.75 (0.0869)	-0.07 (0.9028)	-14.54	-3.8	-15.33	-4.1
	Children	408.67 (0.0000)	-0.46 (0.0461)	-15.81 (0.1406)	-0.7239 (0.2760)	-24.49	-6.6	-33.18	-9.0
	Adult	478.78 (0.0000)	-1.11 (0.0000)	-13.13 (0.1197)	-0.07 (0.8957)	-14.00	-3.5	-14.86	-3.9
	Elderly	468.67 (0.0000)	-1.97 (0.0000)	-23.26 (0.0091)	1.55 (0.0044)	-4.67	-1.4	13.92	4.3
Upper RTI	Total	474.19 (0.0000)	-0.76 (0.0000)	-13.21 (0.0192)	0.28 (0.4297)	-9.88	-2.4	-6.55	-1.6
	Children	351.79 (0.0000)	-0.51 (0.0009)	-14.82 (0.0280)	-0.17 (0.6860)	-16.90	-5.2	-18.98	-5.9
	Adult	539.41 (0.0000)	-0.95 (0.0000)	-11.50 (0.1243)	0.05 (0.9113)	-10.88	-2.3	-10.25	-2.2
	Elderly	544.54 (0.0000)	-1.02 (0.0000)	-18.42 (0.0000)	1.75 (0.0000)	2.58	0.5	23.57	5.1
Lower RTI	Total	811.38 (0.0000)	-0.23 (0.0461)	-24.11 (0.0002)	0.28 (0.4352)	-20.74	-2.6	-17.38	-2.2
	Children	661.69 (0.0000)	-0.71 (0.4364)	-19.42 (0.5117)	-1.42 (0.5798)	-36.47	-5.6	-53.53	-8.3
	Adult	864.43 (0.0000)	-0.14 (0.0000)	-19.16 (0.0000)	0.16 (0.0800)	-21.12	-2.5	-23.10	-2.7
	Elderly	799.52 (0.0000)	-0.14 (0.0000)	-8.34 (0.0000)	0.60 (0.0000)	-1.13	-0.1	6.09	0.8

RTI group		Estimate of intercept	Pre-QP trend (*p*-value)	Change in level (*p*-value)	Change in post-QP trend (*p*-value)	Absolute change post 12 months	Relative change (%) post 12 months	Absolute change post 24 months	Relative change (%) post 24 months
Viral respiratory infection	Total	139.93 (0.0000)	-0.70 (0.0000)	-8.36 (0.2217)	0.39 (0.3565)	-3.72	-4.0	0.92	1.1
	Children	66.59 (0.0000)	-0.38 (0.0000)	-8.11 (0.0036)	0.24 (0.1496)	-5.29	-10.5	-2.47	-5.4
	Adult	178.60 (0.0000)	-0.89 (0.0000)	-16.32 (0.0002)	0.89 (0.0006)	-5.69	-4.8	4.94	4.6
	Elderly	231.05 (0.0000)	-0.92 (0.0293)	-1.28 (0.9508)	-0.43 (0.7285)	-6.44	-3.6	-11.61	-7.0

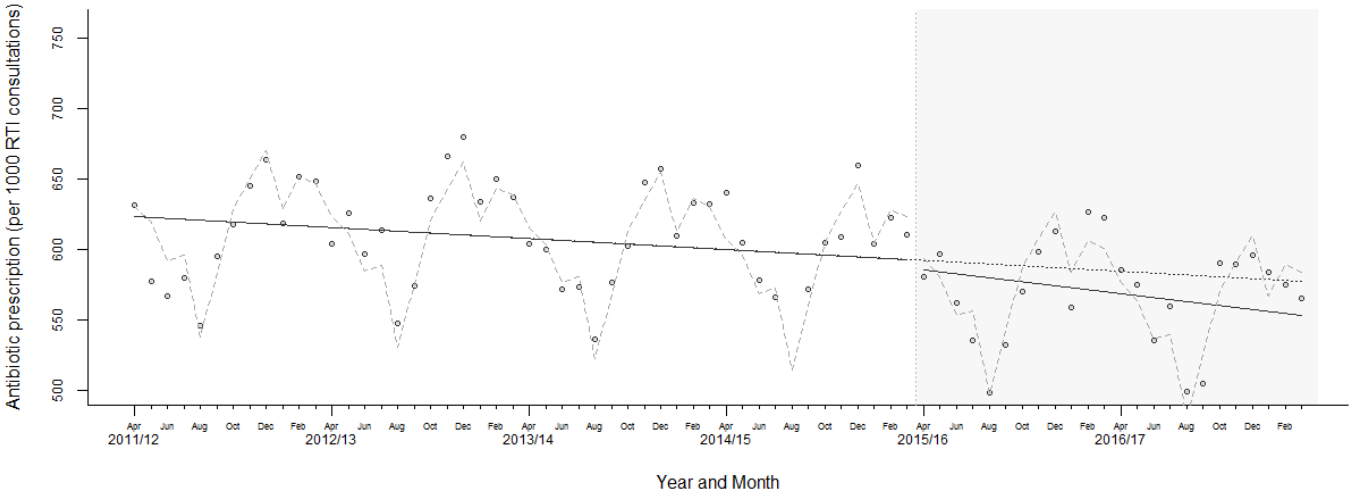
Appendix 29. Time series analysis of antibiotic prescribing for Acute otitis Media by different children age categories (Chapter 4, Page 1 of 2)

Prescribing measure, 2011/12 - 2016/17 (item/per 1000 RTI consultation)	Estimate of intercept	Pre-QP trend (*p*-value)	Change in level (*p*-value)	Change in post-QP trend (*p*-value)	Absolute change post 12 months	Relative change (%) post 12 months	Absolute change post 24 months	Relative change (%) post 24 months
Sensitivity analysis:								
AOM: Children <2 years	682.04 (<0.0001)	-0.23 (<0.0001)	2.25 (0.4393)	-0.53 (0.0122)	-4.08	-0.6	-10.41	-1.4
AOM: Children 2-4 years	631.63 (<0.0001)	-0.65 (0.0031)	-5.45 (0.6007)	-0.76 (0.2349)	-14.60	-2.4	-23.75	-3.9
AOM: Children <5 years	652.05 (<0.0001)	-0.52 (0.0009)	0.56 (0.9523)	-0.95 (0.0907)	-10.84	-1.7	-22.24	-3.4
AOM: Children 5-15 years	532.75 (<0.0001)	-1.06 (0.0004)	-17.24 (0.1834)	-0.45 (0.5845)	-22.62	-4.6	-27.99	-5.8

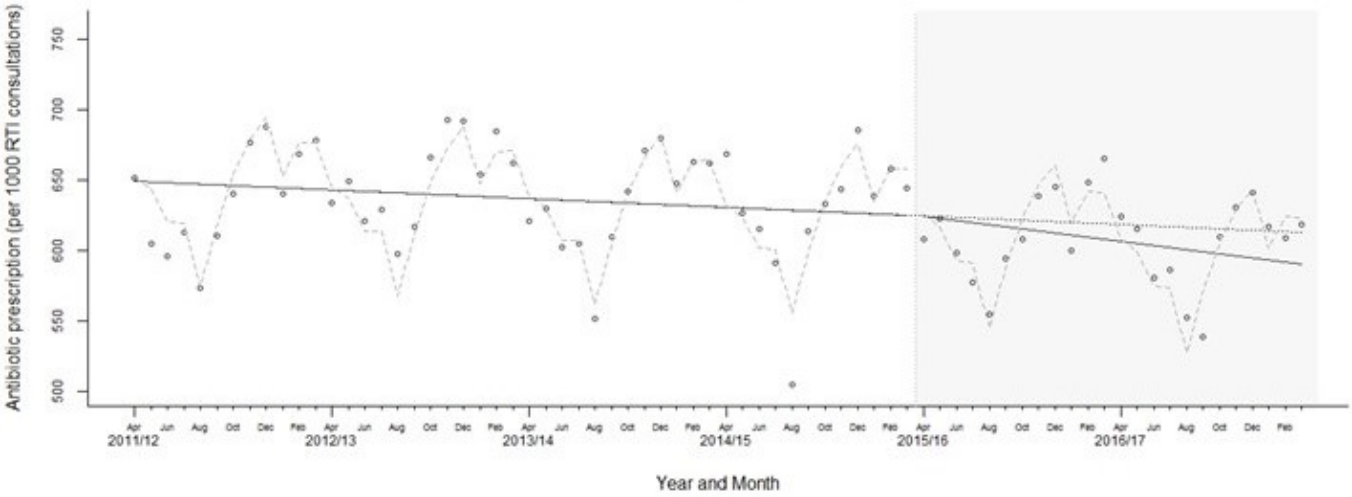
(Table data as seen in Appendix 28*)*



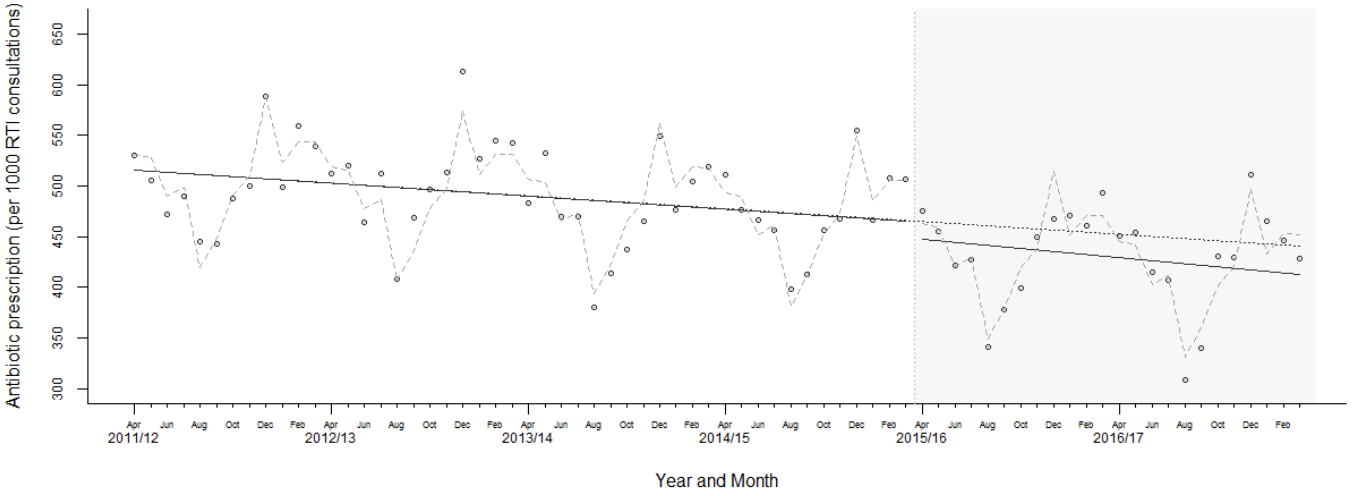
AOM - Children 2 to 4 years



AOM - Children under 5 years

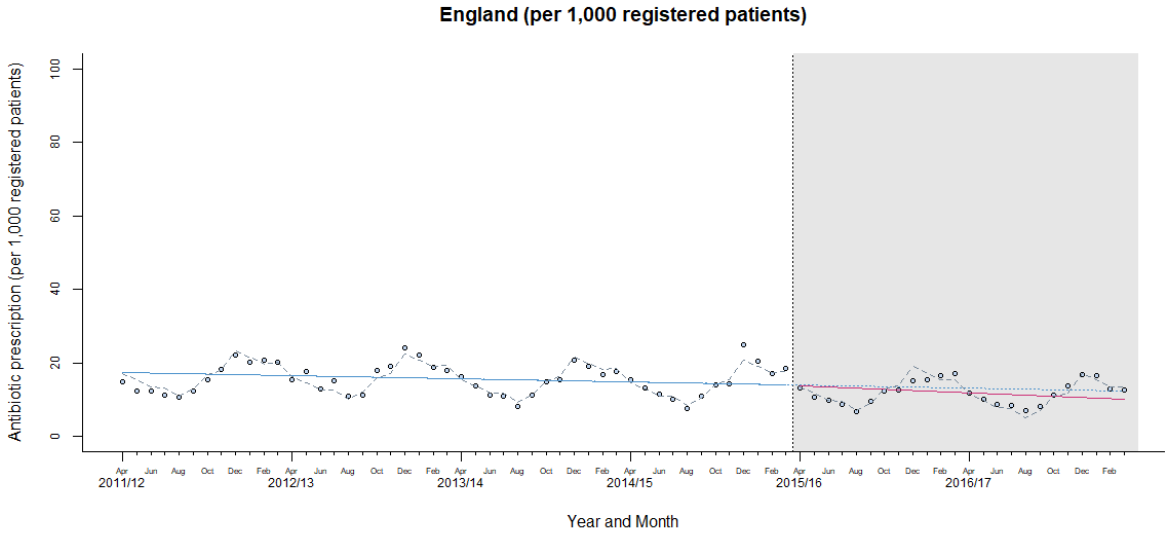


AOM - Children 5 to 15 years

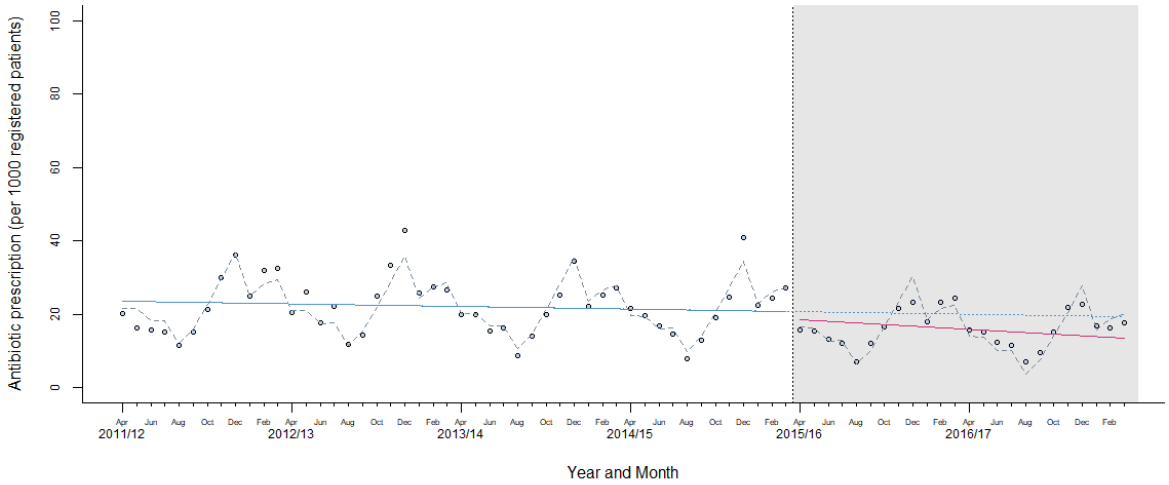


Appendix 30. Time series analysis of antibiotic prescribing by registered patients, for England total and for different age categories (Chapter 4, Page 1 of 2)

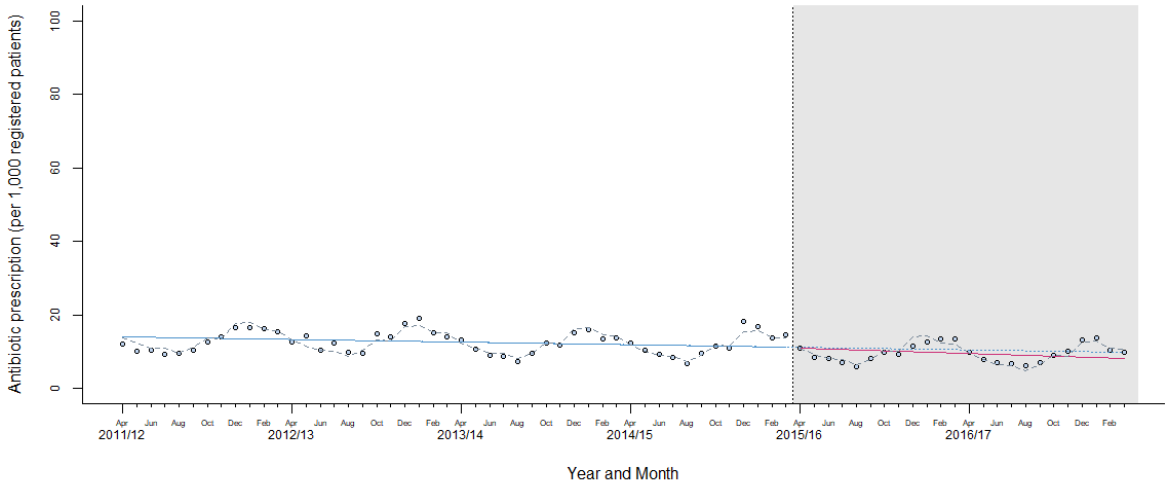
Prescribing measure, 2011/12 - 2016/17		Estimate of intercept	Pre-QP trend (*p*-value)	Change in level (*p*-value)	Change in post-QP trend (*p*-value)	Absolute change post 12 months	Relative change (%) post 12 months	Absolute change post 24 months	Relative change (%) post 24 months
Sensitivity analysis:									
Prescribing per 1,000 registered patients	England total	17.08 (<0.0001)	-0.07 (<0.0001)	-0.07 (0.9316)	-0.10 (0.0621)	-1.22	-7	-2.37	-15
	Children	21.78 (<0.0001)	-0.06 (0.1357)	-2.04 (0.2884)	-0.16 (0.1782)	-3.96	-15.0	-5.9	-22.90
	Adult	13.94 (<0.0001)	-0.06 (<0.0001)	0.00 (0.9990)	-0.07 (0.0653)	-0.80	-6.2	-1.60	-13.02
	Elderly	23.03 (<0.0001)	-0.07 (<0.0001)	-1.90 (0.0597)	0.04 (0.5564)	-1.48	-7.0	-1.06	-5.20



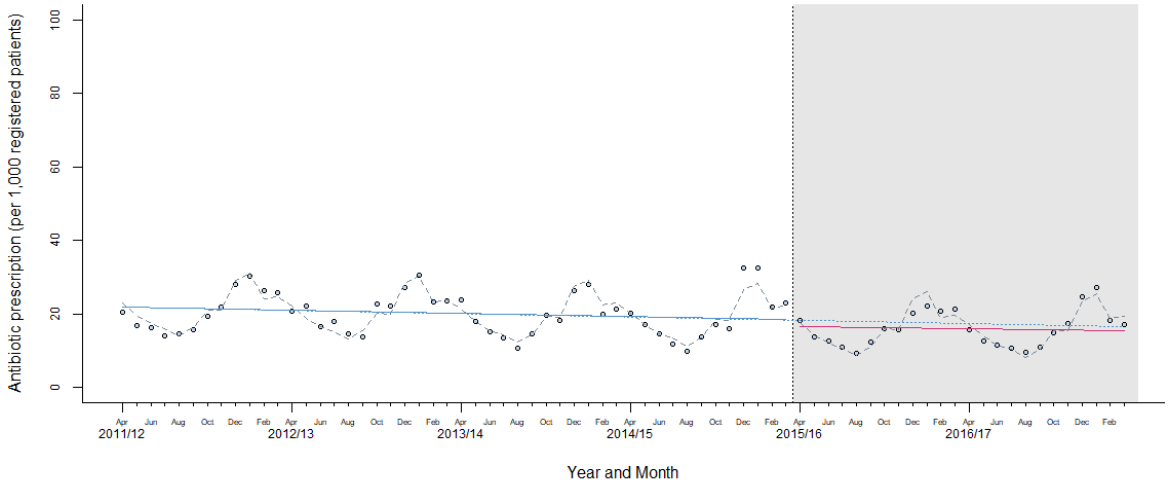
Children (per 1,000 registered patients)



Adults (per 1,000 registered patients)



Elderly (per 1,000 registered patients)



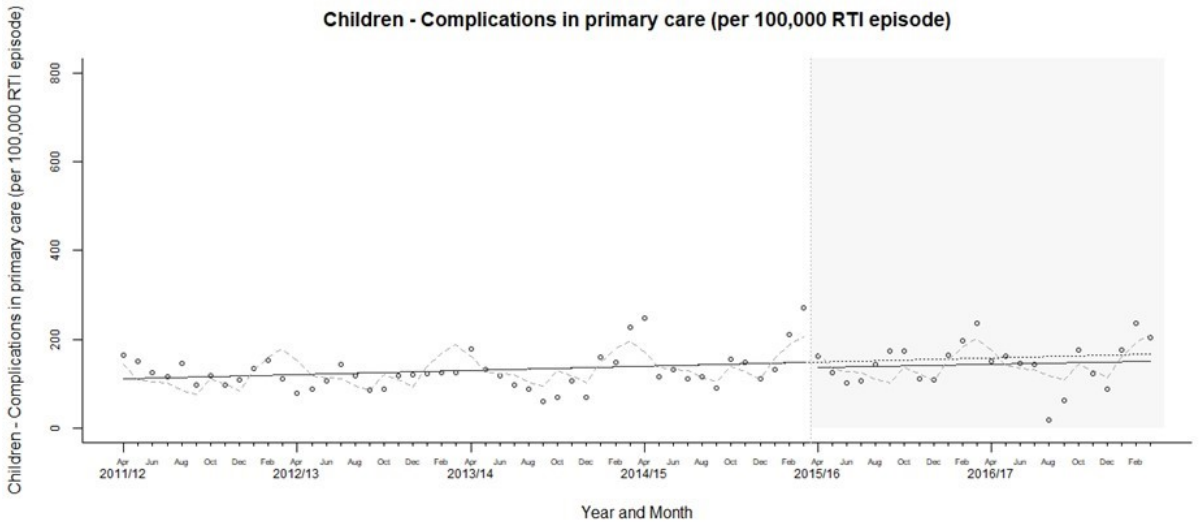
Appendix 31. Re-consultations in primary care: Study population and summary of calculated proportions and rates by financial year and age group, April 2011 to March 2017 (Chapter 5, Page 1 of 1)

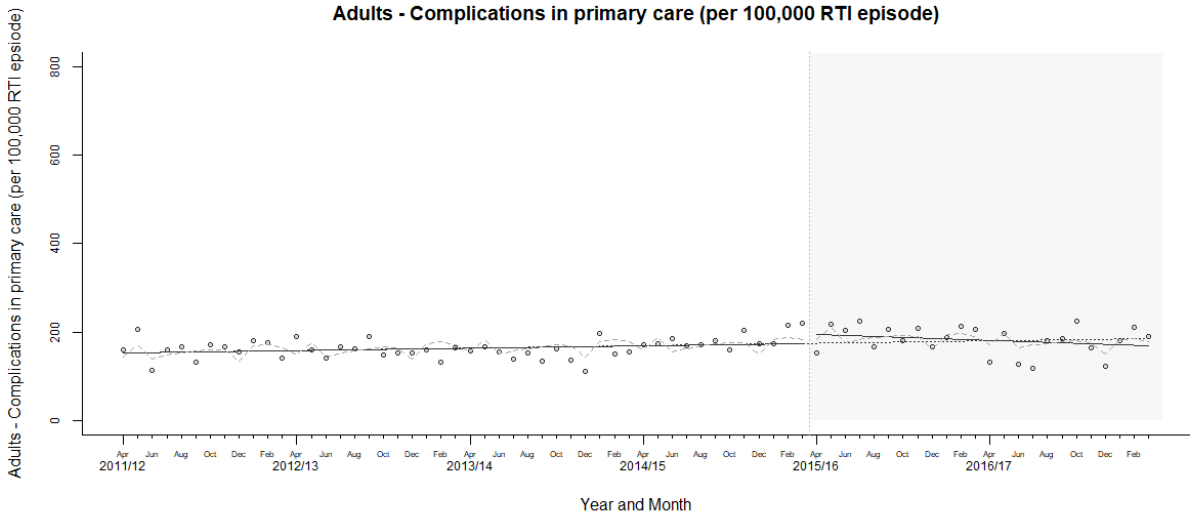
Parameter	Age group	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients	Children	787,822	765,078	727,498	638,421	529,180	369,181
	Adult	2,746,673	2,642,003	2,501,145	2,196,580	1,801,340	1,231,297
	Elderly	701,125	693,036	667,252	604,040	501,736	349,151
Total RTI consultations	Children	473,076	497,250	399,414	349,093	229,696	154,360
	Adult	698,372	734,356	584,377	513,373	338,489	230,840
	Elderly	280,536	290,793	247,921	217,705	144,405	96,744
Index RTI consultations	Children	391,988	411,295	332,896	289,886	193,598	130,674
	Adult	598,155	627,124	502,312	439,979	292,336	199,608
	Elderly	230,364	238,733	204,804	179,096	120,265	80,480
Re-consultations within 30 days of index RTI consultation	Children	68,271	72,260	56,141	49,942	30,689	20,227
	Adult	84,575	90,293	69,403	61,999	39,130	26,552
	Elderly	41,592	43,300	35,826	32,136	20,255	13,612
Re-consultations within 30 days as a proportion of the total index RTI consultations, %	Children	17.42	17.57	16.86	17.23	15.85	15.48
	Adult	14.14	14.40	13.82	14.09	13.39	13.30
	Elderly	18.05	18.14	17.49	17.94	16.84	16.91
Re-consultations within 30 days, per 1000 registered patients	Children	86.66	94.45	77.17	78.23	57.99	54.79
	Adult	30.79	34.18	27.75	28.23	21.72	21.56
	Elderly	59.32	62.48	53.69	53.20	40.37	38.99

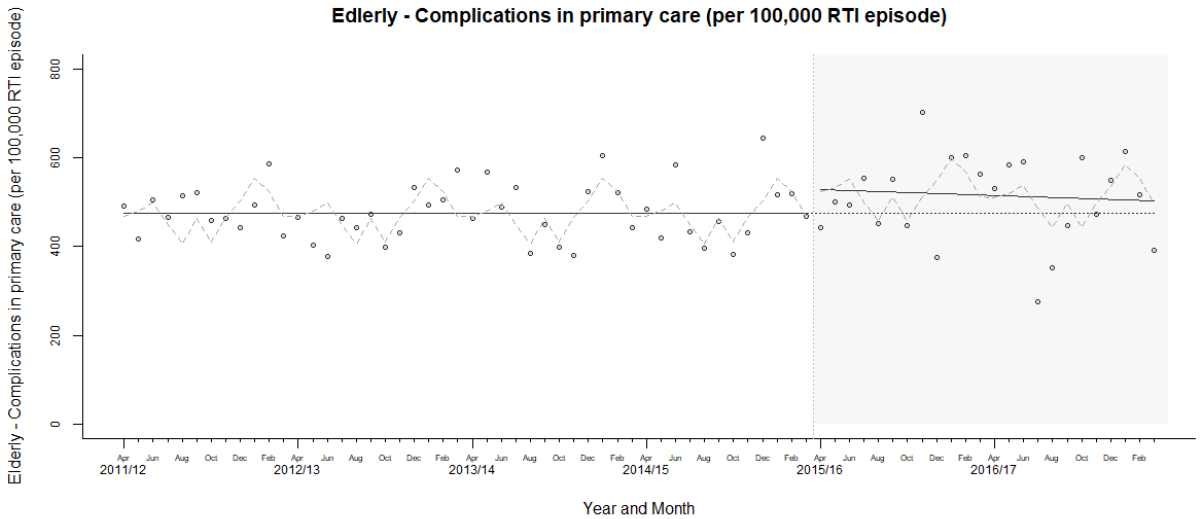
Appendix 32. Complications reported in primary care: Study population and summary of calculated proportions and rates by financial year and age group, April 2011 to March 2017 (Chapter 5, Page 1 of 1)

Parameter	Age group	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients	Children	787,822	765,078	727,498	638,421	529,180	369,181
	Adult	2,746,673	2,642,003	2,501,145	2,196,580	1,801,340	1,231,297
	Elderly	701,125	693,036	667,252	604,040	501,736	349,151
Total RTI episodes	Children	391,988	411,295	332,896	289,886	193,598	130,674
	Adult	598,155	627,124	502,312	439,979	292,336	199,608
	Elderly	230,364	238,733	204,804	179,096	120,265	80,480
Count of complications within 30 days of index RTI consultation	Children	489	458	413	458	295	190
	Adult	962	994	763	808	566	337
	Elderly	1,110	1,112	996	877	629	408
RTI episodes, per 1,000 registered patients	Children	497.56	537.59	457.59	454.07	365.85	353.96
	Adult	217.77	237.37	200.83	200.30	162.29	162.11
	Elderly	328.56	344.47	306.94	296.50	239.70	230.50
Complications within 30 days, per 100,000 registered patients	Children	62.07	59.86	56.77	71.74	55.75	51.47
	Adult	35.02	37.62	30.51	36.78	31.42	27.37
	Elderly	158.32	160.45	149.27	145.19	125.36	116.85
Complications within 30 days, per 100,000 RTI episode	Children	62.07	59.86	56.77	71.74	55.75	51.47
	Adult	35.02	37.62	30.51	36.78	31.42	27.37
	Elderly	158.32	160.45	149.27	145.19	125.36	116.85

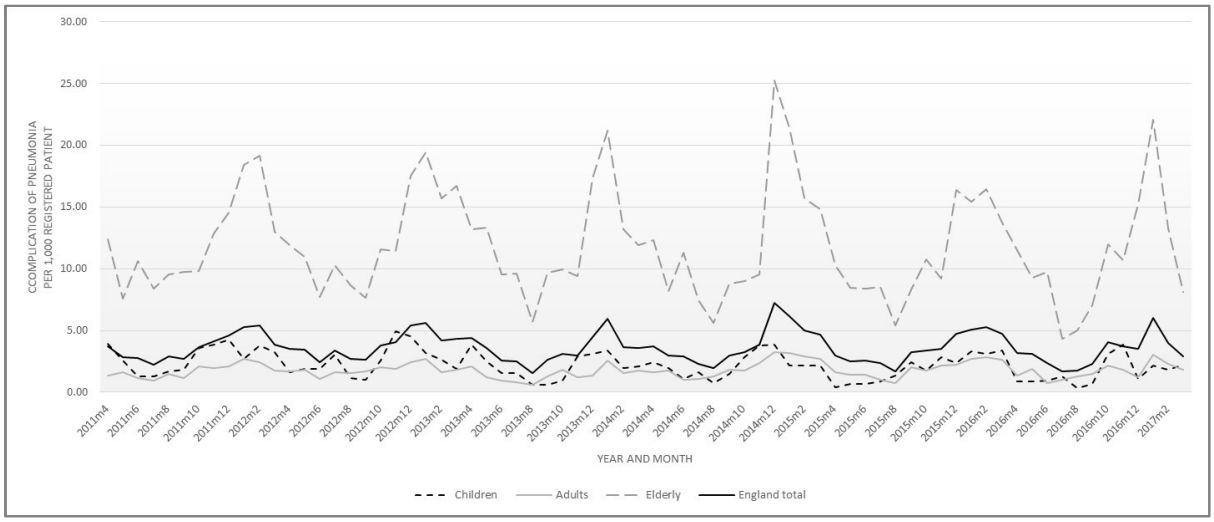
Appendix 33. Interrupted time series analyses of primary care complications within 30-days, by age group per 100,000 RTI episodes, April 2011 to March 2017 (Chapter 5, Page 1 of 1)



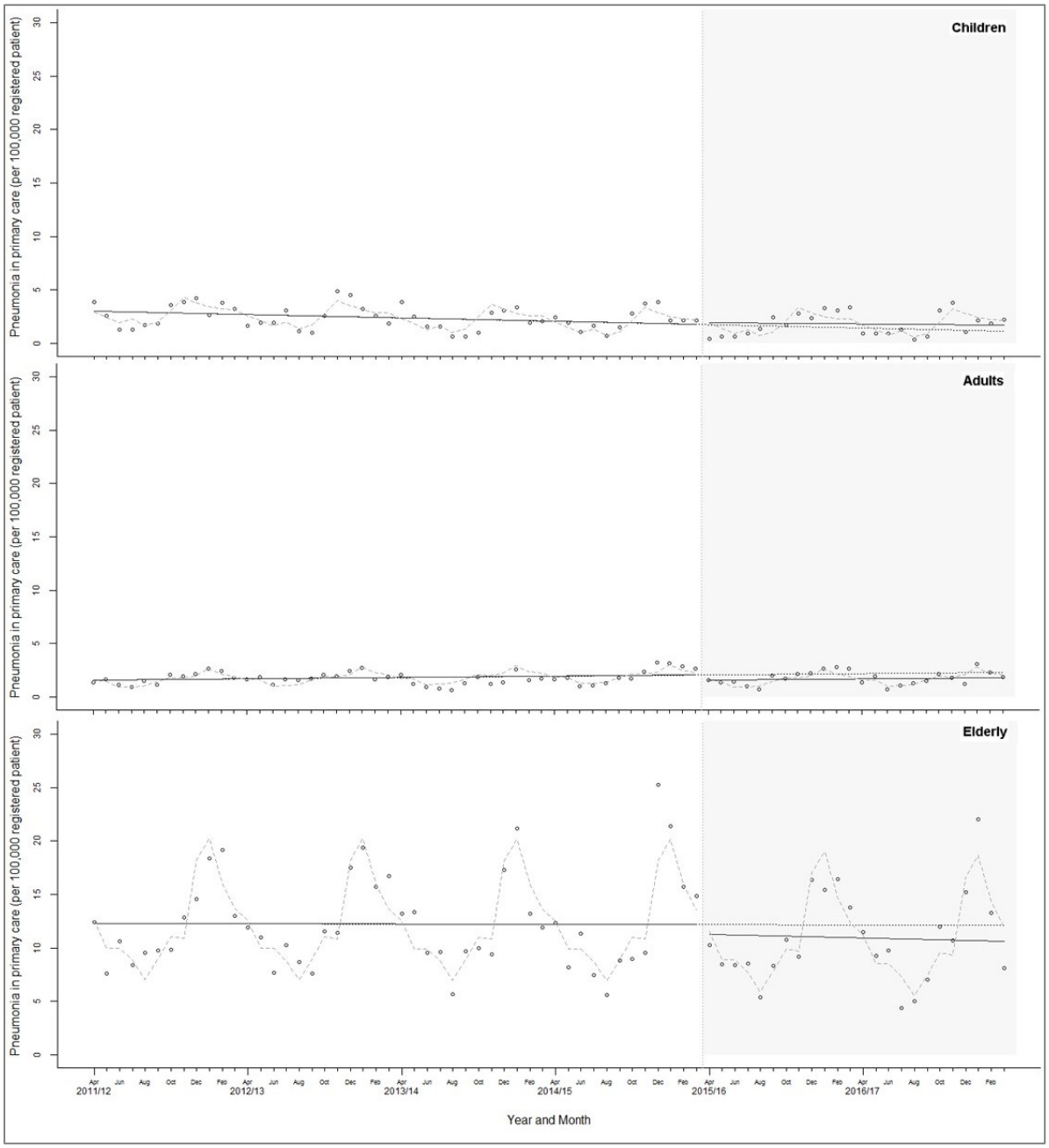




Appendix 34. Trends of pneumonia reported in primary care within 30 days of index RTI infection, total and by age group



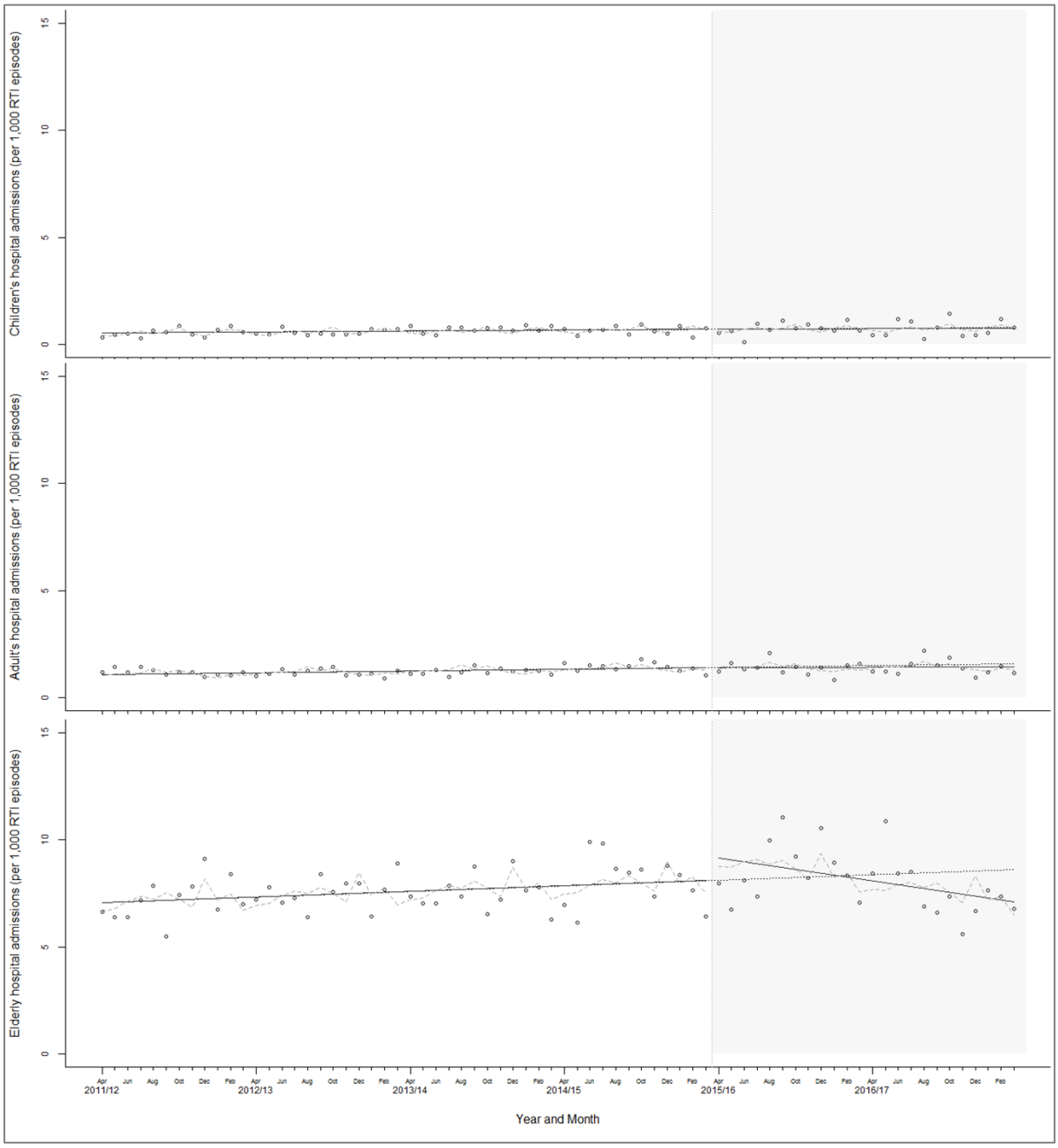
Appendix 35. Interrupted time series analyses of primary care pneumonia within 30-day follow-up, by age group, April 2011 to March 2017 (Chapter 5, Page 1 of 1)



Appendix 36. Complications in secondary care: Study population and summary of calculated proportions and rates by financial year and age group, April 2011 to March 2017 (Chapter 5, Page 1 of 1)

Parameter	Age group	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients eligible for HES linkage	Children	638,644	618,130	587,186	505,639	413,881	292,398
	Adult	2,198,743	2,105,433	1,988,103	1,712,947	1,387,175	956,383
	Elderly	567,732	558,789	537,974	480,083	392,293	272,979
RTI patients with an infectious episode, who were eligible for HES linkage	Children	201,655	208,257	170,804	148,312	102,926	71,118
	Adult	370,165	386,168	312,048	269,902	183,956	126,900
	Elderly	129,530	133,942	115,702	101,334	69,258	46,331
Total RTI episodes of patients eligible for HES linkage	Children	316,798	331,098	265,959	227,626	151,812	104,077
	Adult	483,231	505,535	402,528	346,365	230,449	158,244
	Elderly	186,252	192,317	163,701	140,908	93,597	62,121
Hospital admission within 30 days of index RTI - 1˚ diagnosis code	Children	96	104	97	74	59	43
	Adult	314	329	295	291	192	129
	Elderly	724	800	671	639	437	247
Hospital admission within 30 days of index RTI - 1st hospital episode codes	Children	175	185	190	142	113	75
	Adult	564	581	487	492	315	215
	Elderly	1,355	1,451	1,226	1,129	801	473
Hospital admissions within 30 days, per 100,000 registered patients (eligible for linkage)	Children	27.40	29.93	32.36	28.08	27.30	25.65
	Adult	25.65	27.60	24.50	28.72	22.71	22.48
	Elderly	238.67	259.67	227.89	235.17	204.18	173.27
Hospital admissions within 30 days, per 1,000 RTI episodes	Children	0.55	0.56	0.71	0.62	0.74	0.72
	Adult	1.17	1.15	1.21	1.42	1.37	1.36
	Elderly	7.28	7.54	7.49	8.01	8.56	7.61

Appendix 37. Interrupted time series analyses of hospital admissions for complications within 30-day follow-up, by age group (per 1,000 RTI episodes), April 2011 to March 2017 (Chapter 5, Page 1 of 1)



Appendix 38. All-cause mortality: Study population and summary of calculated rates by financial year and age, April 2011 to March 2017 (Chapter 5, Page 1 of 1)

Parameter	Age group	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients eligible for ONS linkage	Adult	2,198,743	2,105,433	1,988,103	1,712,947	1,387,175	956,383
	Elderly	567,732	558,789	537,974	480,083	392,293	272,979
Total RTI episodes of patients eligible for ONS linkage	Adult	483,231	505,535	402,528	346,365	230,449	158,244
	Elderly	186,252	192,317	163,701	140,908	93,597	62,121
All-cause mortality within 30 days of index RTI*	Adult	217	243	199	178	99	57
	Elderly	2,074	2,133	1,620	1,549	939	542
Mortality related to infectious complication within 30 days of index RTI	Adult	58	57	49	38	27	19
	Elderly	858	971	631	637	342	180
All-cause mortality within 30 days, per 100,000 registered patients	Adult	2.64	2.71	2.46	2.22	1.95	1.99
	Elderly	151.13	173.77	117.29	132.69	87.18	65.94
All-cause mortality within 30 days, per 1,000 RTI episodes	Adult	0.12	0.11	0.12	0.11	0.12	0.12
	Elderly	4.61	5.05	3.85	4.52	3.65	2.90

*Values for the children's age category are not provided due to small cell count.

J Antimicrob Chemother 2018; **73**: 2883–2892
doi:10.1093/jac/dky237 Advance Access publication 28 June 2018

Antimicrobial Chemotherapy

Age-related decline in antibiotic prescribing for uncomplicated respiratory tract infections in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis

Sabine Bou-Antoun[1,2]*, Ceire Costelloe[1], Kate Honeyford[1,2], Mahsa Mazidi[2], Benedict W. J. Hayhoe[2], Alison Holmes[1], Alan P. Johnson[1,3] and Paul Aylin[1,2]

[1]*NIHR Health Protection Research Unit, Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, London, UK;* [2]*Department of Primary Care and Public Health, Imperial College London, London, UK;* [3]*Department of Healthcare-Associated Infections and Antimicrobial Resistance, National Infection Service, Public Health England, London, UK*

*Corresponding author. Tel: +44-20-7594-0788; E-mail: s.bou-antoun15@imperial.ac.uk

Received 23 February 2018; returned 27 April 2018; revised 9 May 2018; accepted 22 May 2018

Objectives: To assess the impact of the 2015/16 NHS England Quality Premium (which provided a financial incentive for Clinical Commissioning Groups to reduce antibiotic prescribing in primary care) on antibiotic prescribing by General Practitioners (GPs) for respiratory tract infections (RTIs).

Methods: Interrupted time series analysis using monthly patient-level consultation and prescribing data obtained from the Clinical Practice Research Datalink (CPRD) between April 2011 and March 2017. The study population comprised patients consulting a GP who were diagnosed with an RTI. We assessed the rate of antibiotic prescribing in patients (both aggregate and stratified by age) with a recorded diagnosis of uncomplicated RTI, before and after the implementation of the Quality Premium.

Results: Prescribing rates decreased over the 6 year study period, with evident seasonality. Notably, there was a 3% drop in the rate of antibiotic prescribing (equating to 14.65 prescriptions per 1000 RTI consultations) ($P < 0.05$) in April 2015, coinciding with the introduction of the Quality Premium. This reduction was sustained, such that after 2 years there was a 3% decrease in prescribing relative to that expected had the pre-intervention trend continued. There was also a concurrent 2% relative reduction in the rate of broad-spectrum antibiotic prescribing. Antibiotic prescribing for RTIs diagnosed in children showed the greatest decline with a 6% relative change 2 years after the intervention. Of the RTI indications studied, the greatest reductions in antibiotic prescribing were seen for patients with sore throats.

Conclusions: Community prescribing of antibiotics for RTIs significantly decreased following the introduction of the Quality Premium, with the greatest reduction seen in younger patients.

Introduction

There is widespread recognition that antibiotic use is a major driver of the emergence and spread of bacterial antibiotic resistance. This has highlighted the importance of antibiotic stewardship, which seeks to reduce unnecessary use of antibiotics in order to conserve the effectiveness of those currently available.[1] Particular emphasis is placed on primary care, which is the healthcare setting in which the highest level of antibiotic prescribing occurs.[2–4] The majority of patients consulting in primary care present with respiratory tract infections (RTIs), which are also the most common indications for antibiotic prescribing in general practice.[5] RTIs (including otitis media, the common cold, sore throats, cough, acute bronchitis and sinusitis) are predominantly uncomplicated self-limiting infections. Treatment of these infections with antibiotics is often inappropriate as they are unlikely to be of clinical benefit while subjecting patients to adverse side effects such as toxicity and carriage of antibiotic-resistant bacteria.[3,5,6]

There are wide variations in community antibiotic prescribing rates both within the UK and when comparing the UK with other European countries.[2,7] Community consumption of antibiotics in the UK (2016: 19.6 DDDs per 1000 inhabitants per day), although

lower than the European average (21.9 DDDs per 1000 inhabitants per day), is still much higher than prescription rates seen in some European countries (e.g. the Netherlands 10.4, Sweden 12.0 and Germany 14.1 DDDs per 1000 inhabitants per day), suggesting that further reductions can be made.[7]

A range of antibiotic stewardship, educational and policy interventions have been implemented in England, aimed at improving the quality of antibiotic prescribing.[1,8] One such initiative, introduced in April 2015, was the inclusion of an antibiotic prescribing element to the national Quality Premium (QP), which provides financial remuneration to Clinical Commissioning Groups (CCGs) responsible for the planning and commissioning of healthcare services in their region. The antibiotic prescribing component of the 2015/16 QP required CCGs to achieve a reduction of ≥1% in total antibiotic prescribing in primary care and a 10% decrease in the proportion of broad-spectrum antibiotics prescribed, specifically co-amoxiclav, cephalosporins and quinolones, relative to the level of prescribing in 2013/14.[9] The QP for 2016/17 also contained a requirement for CCGs to reduce antibiotic prescribing, although the threshold for total antibiotic prescribing was amended to either a ≥4% reduction from the 2013/14 performance or a level of prescribing equal to or below the England 2013/14 mean performance of 1.161 items per Specific Therapeutic group Age-sex Related Prescribing Units (STAR-PU); the requirement to decrease the proportion of broad-spectrum antibiotics prescribed was maintained at 10%.[10]

This study examined the impact of the QP on antibiotic prescribing for RTIs in primary care in England, using an interrupted time series design, which is often used in the evaluation of 'natural experiments'.[11] The study focused on trends in antibiotic prescribing in patients with a recorded diagnosis of uncomplicated acute RTI after consulting their General Practitioner (GP). This group of infections was selected as they are the most common indication for which antibiotics are inappropriately prescribed in primary care and offer the most scope for improvements in the quality of prescribing. Patients were stratified by age to assess whether changes in prescribing were associated with particular age groups.

Methods

Ethical approval

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research (protocol number 16_129R).

Data source and study population

The Clinical Practice Research Datalink (CPRD) is a large, validated electronic database containing routinely collected longitudinal patient-level primary care medical records. The CPRD covers ~7% of the UK population,[12] with the data being representative of patient demographic characteristics (age, sex and ethnicity).[13,14] Data were extracted from the CPRD by identifying all patients with a diagnosis of RTI recorded using Read codes, a hierarchical classification system that includes codes for clinical signs, symptoms and diagnoses.[13] Acute uncomplicated RTIs were classified as acute otitis media (AOM), rhinosinusitis, sore throats, upper RTIs, lower RTIs (not including pneumonia-related codes), viral RTIs and total respiratory infections (total of all diagnostic codes excluding duplicated codes). We included symptoms and viral infections and were inclusive with the selection of codes in order to increase sensitivity. Diagnostic codes were excluded if they were indicative of a more complicated infection such as pneumonia, for which antibiotic prescribing may be recommended.

The cohort of patients with an RTI was analysed to see whether their consultations resulted in antibiotic prescriptions. A prescription was linked to a patient's consultation if both occurred on the same day. The antibiotic therapy codes were identified and categorized using the British National Formulary (BNF) subchapter 5.1, excluding anti-tuberculosis and anti-leprotic drugs.[15]

We included patients with permanent registration status (i.e. excluded temporary residents and visitors), for whom data had been recorded by GPs who met CPRD 'up-to-standard' criteria. This ensured that the included data had been validated to meet reliable quality levels for completeness and recording. Data for individual patients were collected throughout the study period (April 2011 to March 2017), or until the date of transfer of a patient to another general practice, date of death or the date at which the practice had its last collection.

We estimated monthly antibiotic prescription rates (measured as antibiotic items) per 1000 RTI consultations for all practices. The RTI consultation denominator was stratified by age when age-specific rates were being assessed. We compared rates by age group, infection group and antibiotic type (total antibiotics and broad-spectrum antibiotics). Aligned with the QP, broad-spectrum penicillins (including co-amoxiclav), cephalosporins and quinolones were the BNF antibiotic classes used to define broad-spectrum antibiotics. To assess potential differences in antibiotic prescribing by age, the data were split into three age groups: children (under 16 years old), adults (16–64 years old) and the elderly (≥65 years old).

Statistical analyses

Interrupted time series analysis is a strong quasi-experimental research design commonly used for evaluation of longitudinal effects of interventions, and is particularly appropriate for interventions that target population-level health outcomes.[11,16] The analyses used a segmented regression of interrupted time series data to examine the impact of the QP 12 and 24 months after its introduction in England. A monthly time series of the rate of antibiotic prescribing across the study period was used to establish the underlying trend (slope) prior to the introduction of the QP. The observed post-intervention trend line was then compared with the continuation of the pre-intervention trend that would have been expected in the absence of an intervention (the counterfactual), in terms of the change in the trend post-intervention and the change in the level at the intercept (when the QP was introduced, 1 April 2015).[16] The model estimates were then used to quantify the absolute change and relative change at 12 and 24 months. To model possible long-term seasonal patterns, the data were 'time stratified' by month,[17] which permitted adjustment for confounding by seasonality. To account for autocorrelated data, Autoregressive Moving Average (ARMA) models were fitted.[18] The order of the moving average and the autoregressive model parameters were determined using multiple methods including scatter plots of the deviance residuals versus time, the Durbin–Watson test and the autocorrelation and partial autocorrelation functions.[16,17,19] To assess the fit of the model parameters, the maximum likelihood ratio test and quantile–quantile plots were used.[19] Data were tested for heteroscedasticity prior to running the final models using residual plots (standardized residuals versus fitted values) along with Breusch–Pagan tests. The data for the models were homoscedastic.

STATA version 14 (STATA Corp, College Station, TX, USA) was used to perform the data management. The modelling and statistical tests were implemented in R Studio (http://www.r-project.org).

Sensitivity analysis

The QP is an incentivized initiative targeted at the CCG level and not the GP practice level. Therefore the dissemination of information or development

Table 1. Study population and summary of calculated rates by financial year, April 2011 to March 2017

Parameter		2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP-registered patients		4 235 620	4 100 117	3 895 895	3 439 041	2 832 256	1 949 629
Patients who consulted with an RTI included in study		871 406	906 658	750 018	662 462	454 962	309 724
RTI consultations		1 451 984	1 522 399	1 231 712	1 080 171	712 590	481 944
Number of antibiotic items prescribed for RTI		734 137	763 329	602 620	517 236	322 185	214 695
RTI consultation rate, per 1000 registered patients		342.80	371.31	316.16	314.09	251.60	247.20
Rate of antibiotic prescribing for RTIs, per 1000 registered patients		173.32	186.17	154.68	150.40	113.76	110.12
Rate of antibiotic prescribing, per 1000 RTI consultations		505.61	501.40	489.25	478.85	452.13	445.48
Broad-spectrum antibiotic prescribing rate, per 1000 RTI consultations		312.93	307.49	295.05	290.29	268.78	267.44
Broad-spectrum antibiotics as a proportion of the total antibiotics prescribed for RTI, %		69.5	69.3	69.2	69.8	69.2	69.9
Rate of antibiotic prescribing per 1000 RTI consultations, with different recorded diagnoses	AOM	67.56	63.98	64.86	62.17	61.30	60.96
	rhinosinusitis	719.30	705.28	687.31	676.99	648.10	641.49
	sore throat	435.79	434.56	415.28	403.85	374.51	363.78
	upper RTI	454.22	448.98	442.71	429.79	407.84	404.86
	lower RTI	801.20	803.85	791.61	795.11	768.84	770.48
	viral respiratory infection	122.95	126.47	105.18	101.23	82.93	84.81

of local agreements would not necessarily happen instantaneously. To account for this delay, a separate interrupted time series regression model was developed with a 3 month phase-in period. This sensitivity analysis assesses the extent to which the results were influenced by a lag in implementation following the intervention.

Results

GP consultations for RTIs

Between April 2011 and March 2017, a total of 2 198 602 patients [mean age 37.15 years (SD 25.7 years), age range 0–113 years; women, $n = 1\,228\,585$ (55.9%)] who were registered at 431 GP practices across England had 6 480 800 consultations for RTIs. Consultation rates for RTIs of registered patients over the 6 year study period decreased by 28% from 2011/12 (342.80 per 1000 registered patients) to 2016/17 (247.20 per 1000 registered patients). The concurrent rate of registered patients being prescribed antibiotics for RTIs also decreased over these years (36% decrease, from 173.32 to 110.12 per 1000 registered patients) (Table 1). Of the age groups studied, children consulted more often than the other age groups for RTIs (418.11 consultations per 1000 registered patients in 2011/2012 compared with 187.48 and 277.08 per 1000 registered patients for adults and the elderly, respectively) (Table S1, available as Supplementary data at *JAC* Online). Adults were prescribed fewer antibiotics (89.2 prescriptions per 1000 registered patients in 2016/17) compared with children and the elderly (146.9 and 145.1 prescriptions per 1000 registered patients, respectively) (Table S1).

As the QP was aimed at changing prescribing behaviour, we continued the analysis by calculating the antibiotic prescription rate per 1000 RTI consultations. Total antibiotic prescribing (prescription items per 1000 consultations) for all RTIs showed a decreasing trend across the study period (Table 1 and Figure 1) and seasonal fluctuation (Figure 1), with higher rates during the winter months (December) and lower in summer (August).

Reductions in antibiotic prescribing

Figure 1 shows the decrease in the antibiotic prescribing rate (prescription items per 1000 RTI consultations) over the study period. Although the antibiotic prescribing rate was already decreasing by 0.83 prescription items per 1000 RTI consultations per month prior to the introduction of the QP ($P < 0.0001$), there was a 3% drop in the rate (from an estimated counterfactual of 469.2 to 454.6 prescriptions per 1000 RTI consultations), corresponding to a reduction of 14.65 prescriptions per 1000 RTI consultations ($P < 0.05$) that coincided with the implementation of the QP in April 2015. This reduction continued post-QP with no significant change in the slope of the trend (Table 2). Twelve months and 24 months after the introduction of the QP, the average monthly antibiotic prescribing rate was 14.6 per 1000 RTI consultations less than would have been expected had the QP not been introduced. This represents a 3% decrease relative to that expected had the existing trend continued (Table 2).

When the rates were censored around a 3 month implementation period, the change in level was greater and showed a decrease of 21.39 antibiotic items per 1000 consultations ($P < 0.0001$). Owing to reduction in the gradient of the slope post-QP, the drop in level was not sustained and there was no difference in the relative change after 2 years compared with the model without a lag period (Figure 1b and Table 2).

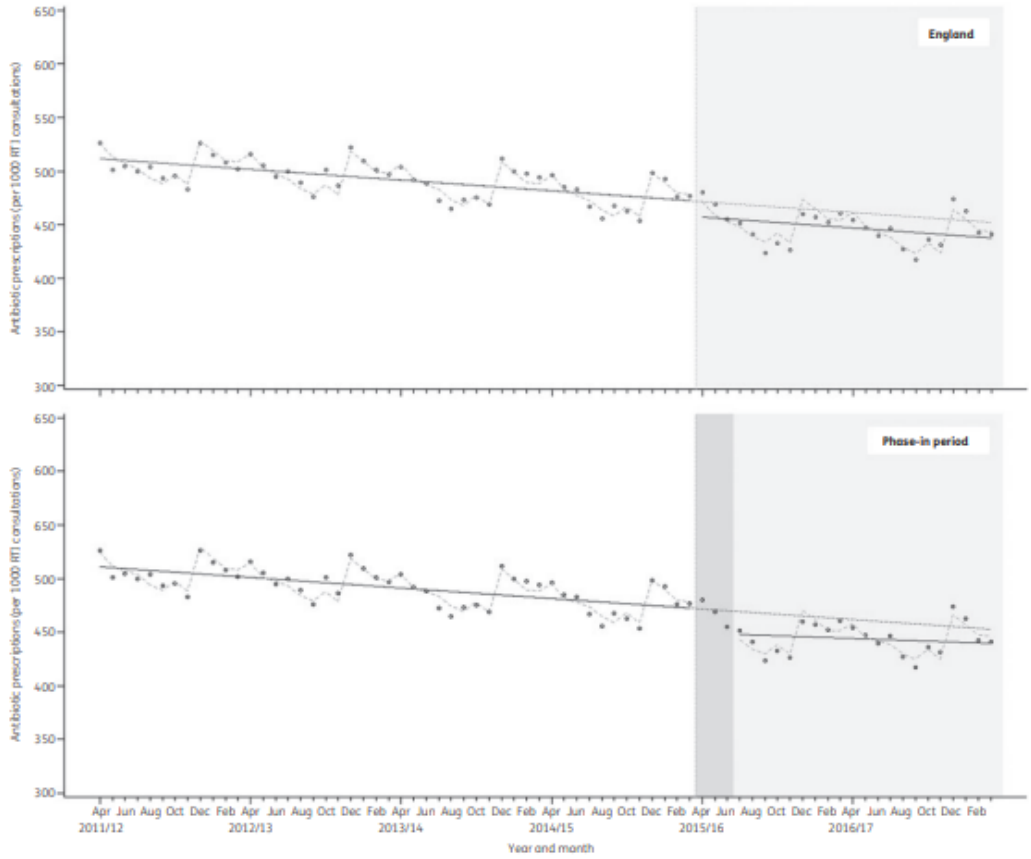


Figure 1. Interrupted time series analyses of the total antibiotic prescription rate for RTI consultations in England, April 2011 to March 2017 and total antibiotic prescription rate with a 3 month phase-in period.

The most commonly prescribed antibiotic group was broad-spectrum penicillins. The prescribing rate for broad-spectrum antibiotics decreased by 8.53 per 1000 consultations per month ($P < 0.05$). Whether this further reduction was sustained below that projected without the QP is questionable as there was a positive change in the post-QP trend; this reduction in the gradient of the post-QP slope was not statistically significant (Figure 2a and Table 2). Prescription of broad-spectrum antibiotics as a proportion of all antibiotic prescriptions did not vary considerably between the years, a finding that was consistently seen in all age groups (Figure 2b and Table 1).

Changes in antibiotic prescribing by age

The prescription rate per 1000 consultations was highest in the elderly and lowest in children, who also consult the most often (elderly 523.69, adults 475.66 and children 351.32 per 1000 consultations in 2016/17) (Table S1 and Figure 3).

The age-stratified interrupted time series analysis illustrates that the impact of the QP differed across the three age groups, with the greatest reduction in antibiotic prescribing for RTIs occurring in children (Table 2). Two years after implementation of the QP, there was a 6% reduction in the rate of antibiotic prescribing for children relative to that expected had the pre-QP trend continued. At implementation of the QP, the rate of antibiotic prescribing fell across all the age groups, with the largest change seen in the adult category (decrease of 16 per 1000 consultations, compared with 12.71 per 1000 consultations in children and 12.32 per 1000 consultations in the elderly) (Figure 3 and Table 2). The interrupted time series graphs illustrate that only the prescription rate in children seemed to be widening from the counterfactual prescription

Table 2. Findings from the interrupted time series analyses on the change in trend and level of antibiotic prescribing for RTIs and the relative and absolute changes post-QP

Prescribing measure, 2011/12–2016/17 (item per 1000 RTI consultations)		Estimate of intercept (*P*)	Pre-QP trend (*P*)	Change in level (*P*)	Change in post-QP trend (*P*)	Absolute change 12 months post-QP	Relative change 12 months post-QP (%)	Absolute change 24 months post-QP	Relative change 24 months post-QP (%)
England antibiotic prescribing		526.73 (<0.0001)	−0.83 (<0.0001)	−14.65 (0.0022)	0.0018 (0.9950)	−14.62	−3	−14.60	−3
Broad-spectrum antibiotic prescribing		321.18 (<0.0001)	−0.76 (<0.0001)	−8.53 (0.0022)	0.29 (0.0727)	−5.62	−2	−1.37	−0.5
Subgroup analyses									
age group	children	418.85 (<0.0001)	−0.62 (0.0002)	−12.71 (0.0553)	−0.47 (0.3091)	−18.31	−5	−23.91	−6
	adult	560.83 (<0.0001)	−0.91 (<0.0001	−16.00 (0.0007)	0.17 (0.5315)	−18.03	−4	−20.05	−4
	elderly	598.70 (<0.0001)	−1.02 (<0.0001)	−12.32 (0.002)	1.05 (<0.0001)	0.23	0	12.77	2
RTI group	AOM	65.80 (<0.0001)	−0.11 (0.0126)	−0.36 (0.8603)	−0.02 (0.8827)	0.58	1	0.81	1
	rhinosinusitis	729.26 (<0.0001)	−0.62 (0.0002)	−12.71 (0.0553)	−0.47 (0.3091)	−6.36	−1	−5.91	−1
	sore throat	462.08 (<0.0001)	−1.04 (<0.0001)	−13.75 (0.0869)	−0.07 (0.9028)	−14.54	−4	−15.33	−4
	upper RTI	474.19 (<0.0001)	−0.76 (<0.0001)	−13.21 (0.0192)	0.28 (0.4297)	−9.88	−2	−6.55	−2
	lower RTI	811.38 (<0.0001)	−0.23 (0.0461)	−24.11 (0.0002)	0.28 (0.4352)	−20.74	−3	−17.38	−2
	viral respiratory infection	139.93 (<0.0001)	−0.70 (<0.0001)	−8.36 (0.2217)	0.39 (0.3565)	−3.72	−4	0.92	1
Sensitivity analysis									
3 month phase-in period, England antibiotic prescribing		525.08 (<0.0001)	−0.82 (<0.0001)	−21.39 (<0.0001)	0.44 (0.1186)	−19.86	−4.2	−14.53	−3.15

rate trend as time progressed, owing to the change in the children's post-QP trend, which further declined by 0.47 per 1000 consultations (children's post-QP trend was declining by 1.09 compared with 0.62 pre-QP, $P > 0.05$).

Changes in antibiotic prescribing by RTI group

The most commonly reported codes for a consultation were for upper RTIs, with 54% of consultations referring to such an infection. Of the total antibiotic prescriptions, 48% were prescribed for upper RTIs. Antibiotic prescribing for upper RTI consultations in adults and the elderly were higher than in children (Figure S1). However, prescribing in children showed the greatest decrease in absolute and relative change (Figure S1 and Table S2), with the time series for the elderly showing a shift post-QP to an increase in antibiotic prescribing compared with the pre-QP trend. Adults and the elderly had greater antibiotic prescription rates in all infection groups apart from AOM, which was highest in children, particularly children aged <2 years old. Further analyses into prescribing for AOM revealed that there was no significant change post-QP in the level of antibiotic prescribing for children <2 years old. Reductions in the level and trend of prescribing in children for AOM was most evident in children aged 5–15 years.

Consultations for lower RTIs and rhinosinusitis resulted in the greatest rate of antibiotic prescribing, as shown by the highest estimate of the intercepts in Table 2. Sore throats and lower RTI consultations had the greatest decline in the level of antibiotic prescribing post-QP compared with the other infection groups (Table 2 and Figure 4), with a 4% and 3% decline, respectively, in antibiotic prescriptions per 1000 consultations relative to the counterfactual expected rate at the same point in time. The majority of the reductions in the sore throat and the lower RTI groups were influenced by the decreases in the level and trend post-QP seen in children (Figure S1 and Table S2).

Rhinosinusitis-related consultations showed an overarching decrease in antibiotic prescribing over time. The greatest reductions in absolute change were seen in children across all infection groups, apart from rhinosinusitis (Table S2), where there was an increased change in level (16.61 per 1000 consultations) and trend [1.47 per 1000 consultations ($P < 0.05$)].

Discussion

Following the introduction of the QP in April 2015 we observed a decreasing trend in antibiotic prescribing for RTIs in primary care, with seasonal peaks in the winter period and troughs in the summer. There was a significant drop in the level of this trend by 14.65 antibiotic items per 1000 consultations in April 2015 ($P < 0.05$), coinciding with the introduction of the QP. A year after the implementation of the QP there was a 3% relative reduction below the level of antibiotic prescribing for RTI consultations expected in the absence of this intervention. Our findings suggest that this decline was sustained after 2 years. Similarly there was a level drop in the rate of broad-spectrum antibiotic prescribing, although no differences were seen in the proportions of broad-spectrum antibiotics prescribed.

The rate of antibiotic prescribing across the study period was highest in adults for the majority of RTIs and lowest in children, apart from for AOM, an infection most commonly seen in the

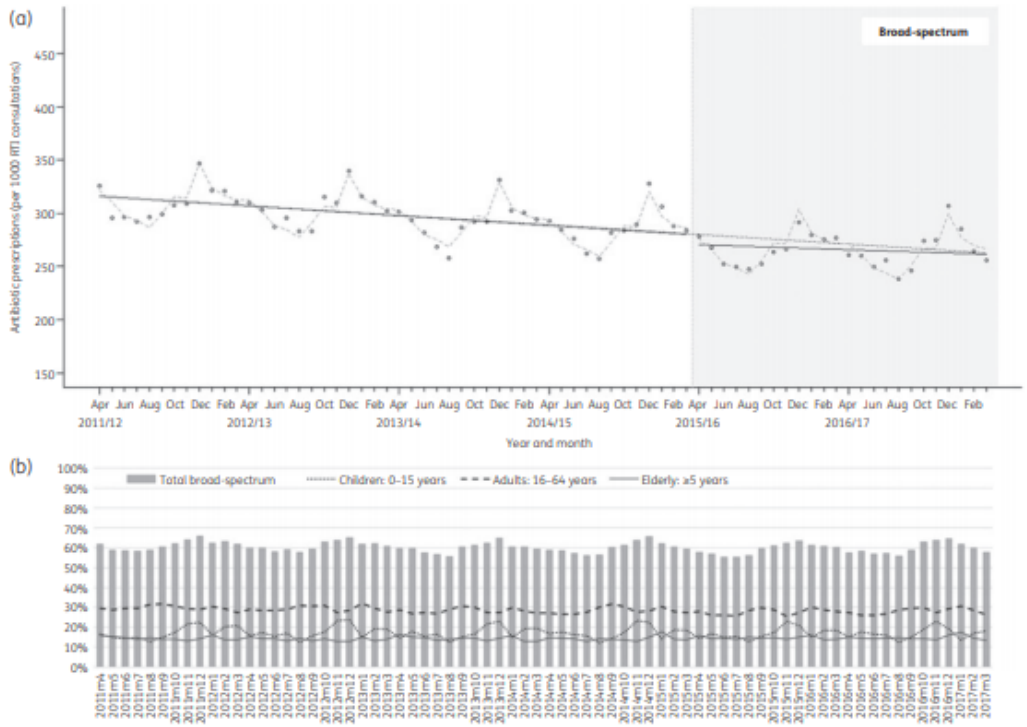


Figure 2. (a) Interrupted time series analysis of broad-spectrum antibiotic prescription rate for RTI consultations in England, April 2011 to March 2017. (b) Proportion of broad-spectrum antibiotics prescribed, by age group.

young. This may be because adults attend with more pronounced or more numerous symptoms, and are better able to communicate subjective symptoms.[20] However, overall antibiotic prescribing for RTIs in children exhibited the greatest decline, with a 6% relative change in this age group 2 years post-QP. These reductions in prescribing for children were predominantly for upper RTI-, sore throat- and lower RTI-related consultations (6%, 9% and 8% relative change 24 months post-QP, respectively). RTIs are more common in children, particularly those younger than 4 years, as they are immunologically naive and have an increased tendency to develop infections.[20] This, along with parental anxiety regarding their child's infection, may be responsible for the higher rates of consultations in this age group,[21] with research suggesting that two-thirds of young children visit their GP with an acute RTI at least once a year.[21] Doctors' concern around potential complications when a bacterial infection is not treated, difficulty in establishing a clinical diagnosis and perceived parental expectations may have contributed to high prescribing rates for RTIs in children.[20] Along with growing GP and patient awareness of antibiotic stewardship, the introduction of the pneumococcal conjugate vaccine in recent years may have decreased the perceived risk of bacterial infections in children.[22] It would therefore be expected that the greatest reductions in antibiotic prescribing, as has been seen in this study, would be made in children for self-limiting indications such as upper RTIs and sore throats. Assessment of the underlying lower RTI Read codes revealed that there have been reductions in prescribing for bronchial cough, acute bronchitis and bronchiolitis, and acute tracheitis consultations. The decrease in the rate of antibiotic prescribing for lower RTIs may be of potential concern, as antibiotics may be advisable in certain instances; these findings would benefit further investigation.

The interrupted time series analysis that took account of a 3 month phase-in period suggested that there were greater reductions in the level change post-QP when a lag in the intervention was included. The QP was targeted at CCGs and therefore the time to disseminate information and develop local agreements would vary and they would not necessarily happen instantaneously. There are various mechanisms by which an intervention implemented at the CCG level may impact GP practice-level prescribing behaviour, such as mediated pressure from medicine management teams.[23] Further research on the route(s) of QP translation into primary care activities would be beneficial.

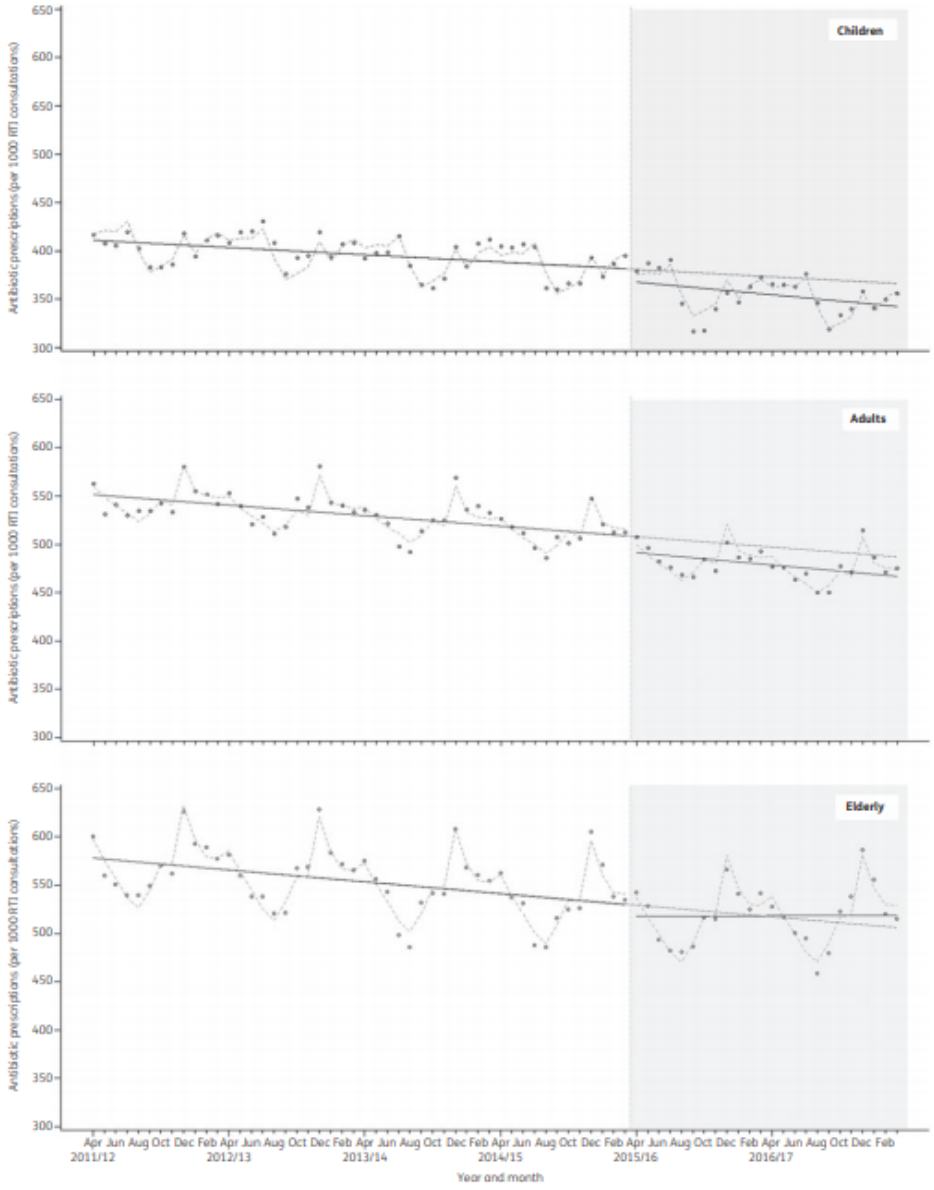


Figure 3. Interrupted time series analyses of antibiotic prescription rate for RTI consultations in England, April 2011 to March 2017, for children, adults and the elderly.

Figure 4. Antibiotic prescription rate for RTI consultations stratified by infection group, April 2011 to March 2017.

An assumption made when using an interrupted time series analysis is that the pre-intervention trend would have continued unchanged in the absence of the intervention of interest and that there are no competing interventions. In addition to the QP, other initiatives, guidance and reports have highlighted the importance of reducing inappropriate antibiotic prescribing.[8] It could therefore be problematic when attempting to discriminate between whether the changes seen were truly an effect of the QP, or a cumulative impact of multiple initiatives. The QP is an NHS England-led national initiative, which provided a financial incentive for reductions in antibiotic prescribing in primary care, an approach which several studies have indicated as being effective in bringing about change in prescribing.[24–26] There are, however, studies that report improvements occurring prior to the schemes and no discernible effects.[27–31] In England, the positive influence of financial incentives on clinical outcomes has been previously shown with the Quality and Outcomes Framework in 2004,[26,32] although positive effects were not universal[27] and there were associated concerns about unintended consequences.[30,33] Our results do show that although a decreasing trend was evident prior to the QP, there was a statistically significant further decrease in antibiotic prescribing, when compared with the expected counterfactual trend had the QP not been introduced.

Previous studies have shown declining trends in both consultation rates and antibiotic prescribing for acute RTIs[34–36] and have suggested that reductions in antibiotic prescribing arose mainly because the rate of infections had been declining.[35] This reduction in consultations is either due to a true decrease in the incidence of RTIs or to the growth in public awareness around health issues, antibiotic consumption and self-management.[34] We used the count of RTI consultations as the denominator for the rate calculations, permitting us to attenuate for changes in consultations and therefore identifying changes to prescribing behaviours in primary care.

A limitation of the data used is that collection is not primarily for research purposes and, as with all routine data, there is an inherent risk of miscoding and misclassification bias owing to differences in the accuracy and completeness of clinical codes used by GPs and/or over time. To reduce selection bias, we were inclusive with the selection of codes, including symptoms, diagnosis codes and viral respiratory infections. Having studied a large number of patients and included practices with good-quality data, the sample is representative of the population in England and generalizable to other countries with similar healthcare settings.[13,14]

A further limitation to be noted is that we were unable to assess whether prescriptions were dispensed or whether a delayed antibiotic prescription was given.

In summary, we have shown that there have been significant reductions in prescribing of antibiotics for RTIs following the implementation of the 2015/16 QP, with the greatest reductions seen in children. Many patients were still prescribed antibiotics for upper RTIs such as sinusitis, AOM and sore throats, which guidance suggests are likely to be self-limiting infections for which antibiotics offer little clinical benefit. Further reductions in primary care antibiotic prescribing should therefore still be achievable. However, it will be important to monitor whether reductions in antibiotic prescribing are associated with any increases in morbidity; such work is currently ongoing.

Acknowledgements

We thank Fran Husson and Tim Sims, who are the patient representatives for the Health Protection Research Unit, for their review of the research proposal for this work.

Funding

The research was funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Imperial College London in partnership with PHE, in collaboration with The Sanger Institute, the University of Cambridge Veterinary School and Imperial College Health Partners.

C. C. is supported by an NIHR Career Development fellowship (CDF-2016-09-015).

A. H. acknowledges the support of the Imperial College Healthcare Trust NIHR Biomedical Research Centre (BRC).

Transparency declarations

None to declare.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health and Social Care or PHE.

Supplementary data

Tables S1 and S2 and Figure S1 are available as Supplementary data at *JAC* Online.

References

1 O'Neill J. *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*. http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.

2 Goossens H, Ferech M, Stichele RV *et al*. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**: 579–87.

3 Petersen I, Hayward AC; on behalf of the SACAR Surveillance Subgroup. Antibacterial prescribing in primary care. *J Antimicrob Chemother* 2007; **60**: i43–7.

4 PHE. *English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR), Report*. 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/362374/ESPAUR_Report_2014__3_.pdf.

5 Centre for Clinical Practice at NICE (UK). *Respiratory Tract Infections—Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care*. London, UK: National Institute for Health and Clinical Excellence, 2008. https://www.ncbi.nlm.nih.gov/pubmed/21698847.

6 Hawker JI, Smith S, Smith GE *et al*. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995–2011: analysis of a large database of primary care consultations. *J Antimicrob Chemother* 2014; **69**: 3423–30.

7 ECDC (An Agency of the European Union). *Summary of the Latest Data on Antibiotic Consumption in the European Union: 2017*. https://ecdc.europa.eu/sites/portal/files/documents/Final_2017_EAAD_ESAC-Net_Summary-edited%20-%20FINAL.with%20erratum.pdf.

8 Hopkins S. UK initiatives to reduce antimicrobial resistant infections, 2013-2018. *Int J Health Gov* 2016; **21**: 131–8.

9 NHS England. *Quality Premium: 2015/16 Guidance for CCGs*. https://www.england.nhs.uk/wp-content/uploads/2013/12/qual-prem-guid.pdf.

10 NHS England. *Quality Premium: 2016/17 Guidance for CCGs*. https://www.england.nhs.uk/wp-content/uploads/2016/03/qualty-prem-guid-2016-17.pdf.

11 Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017; **46**: 348–55.

12 Herrett E, Gallagher AM, Bhaskaran K *et al*. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**: 827–36.

13 Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiol Drug Saf* 2009; **18**: 704–7.

14 Wang Y, Hunt K, Nazareth I *et al*. Do men consult less than women? An analysis of routinely collected UK general practice data. *BMJ Open* 2013; **3**: e003320.

15 Joint Formulary Committee. *British National Formulary*. London, UK: BMJ Group and Pharmaceutical Press, 2015.

16 Wagner AK, Soumerai SB, Zhang F *et al*. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002; **27**: 299–309.

17 Bhaskaran K, Gasparrini A, Hajat S *et al*. Time series regression studies in environmental epidemiology. *Int J Epidemiol* 2013; **42**: 1187–95.

18 Helfenstein U. The use of transfer-function models, intervention analysis and related time-series methods in epidemiology. *Int J Epidemiol* 1991; **20**: 808–15.

19 Box GEP, Jenkins GM, Reinsel GC *et al*. *Time Series Analysis: Forecasting and Control*. Hoboken, NJ, USA: John Wiley & Sons, Inc., 2016.

20 Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. *Cochrane Database Syst Rev* 2016; issue 2: CD007880.

21 Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. *Br J Gen Pract* 2002; **52**: 401–9.

22 Meropol SB, Chen Z, Metlay JP. Reduced antibiotic prescribing for acute respiratory infections in adults and children. *Br J Gen Pract* 2009; **59**: e321–8.

23 PHE. *English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR), Report*. 2017: 105–6. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/656611/ESPAUR_report_2017.pdf.

24 Greene RA, Beckman H, Chamberlain J *et al.* Increasing adherence to a community-based guideline for acute sinusitis through education, physician profiling, and financial incentives. *Am J Manag Care* 2004; **10**: 670–8.

25 Sabuncu E, David J, Bernède-Bauduin C *et al.* Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002–2007. *PLoS Med* 2009; **6**: e1000084.

26 Arrowsmith ME, Majeed A, Lee JT *et al.* Impact of pay for performance on prescribing of long-acting reversible contraception in primary care: an interrupted time series study. *PLoS One* 2014; **9**: e92205.

27 Serumaga B, Ross-Degnan D, Avery AJ *et al.* Effect of pay for performance on the management and outcomes of hypertension in the United Kingdom: interrupted time series study. *BMJ* 2011; **342**: d108.

28 MacBride-Stewart SP, Elton R, Walley T. Do quality incentives change prescribing patterns in primary care? An observational study in Scotland. *Fam Pract* 2008; **25**: 27–32.

29 Bottle A, Millett C, Xie Y *et al.* Quality of primary care and hospital admissions for diabetes mellitus in England. *J Ambul Care Manage* 2008; **31**: 226–38.

30 Campbell SM, Reeves D, Kontopantelis E *et al.* Effects of pay for performance on the quality of primary care in England. *N Engl J Med* 2009; **361**: 368–78.

31 Gillam S, Steel N. The Quality and Outcomes Framework—where next? *BMJ* 2013; **346**: f659.

32 Harrison MJ, Dusheiko M, Sutton M *et al.* Effect of a national primary care pay for performance scheme on emergency hospital admissions for ambulatory care sensitive conditions: controlled longitudinal study. *BMJ* 2014; **349**: g6423.

33 Ashworth M. Quality and Outcomes Framework: time to take stock. *Br J Gen Pract* 2010; **60**: 637–8.

34 Ashworth M, Charlton J, Latinovic R *et al.* Age-related changes in consultations and antibiotic prescribing for acute respiratory infections, 1995–2000. Data from the UK General Practice Research Database. *J Clin Pharm Ther* 2006; **31**: 461–7.

35 Ashworth M, Latinovic R, Charlton J *et al.* Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. *J Public Health (Oxf)* 2004; **26**: 268–74.

36 Gulliford M, Latinovic R, Charlton J *et al.* Selective decrease in consultations and antibiotic prescribing for acute respiratory tract infections in UK primary care up to 2006. *J Public Health (Oxf)* 2009; **31**: 512–20.

Supplementary data

Table S1. Study population and summary of calculated rates by financial year and age group, April 2011 to March 2017

Parameter		2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
CPRD GP registered patients	Children	787,822	765,078	727,498	638,421	529,180	369,181
	Adult	2,746,673	2,642,003	2,501,145	2,196,580	1,801,340	1,231,297
	Elderly	701,125	693,036	667,252	604,040	501,736	349,151
RTI consultations	Children	473,076	497,250	399,414	349,093	229,696	154,360
	Adult	698,372	734,356	584,377	513,373	338,489	230,840
	Elderly	280,536	290,793	247,921	217,705	144,405	96,744
Number of antibiotic items prescribed for RTI	Children	191,184	202,431	156,572	134,904	82,204	54,230
	Adult	381,535	396,391	309,167	264,184	164,665	109,801
	Elderly	161,418	164,507	136,881	118,148	75,316	50,664
RTI consultation rate, per 1,000 registered patients	Children	600.49	649.93	549.02	546.81	434.06	418.11
	Adult	254.26	277.95	233.64	233.71	187.91	187.48
	Elderly	400.12	419.59	371.56	360.41	287.81	277.08
Rate of antibiotic prescribing for RTIs, per 1,000 registered patients	Children	242.67	264.59	215.22	211.31	155.34	146.89
	Adult	138.91	150.03	123.61	120.27	91.41	89.18
	Elderly	230.23	237.37	205.14	195.60	150.11	145.11
Rate of antibiotic prescribing, per 1,000 RTI consultations	Children	404.13	407.10	392.00	386.44	357.88	351.32
	Adult	546.32	539.78	529.05	514.60	486.47	475.66
	Elderly	575.39	565.72	552.12	542.70	521.56	523.69
Broad-spectrum antibiotic prescribing rate, per 1,000 RTI consultations	Children	278.08	278.54	266.37	263.74	239.68	238.25
	Adult	310.89	305.07	291.45	286.18	263.96	261.30
	Elderly	376.75	363.08	349.73	342.57	326.35	328.64

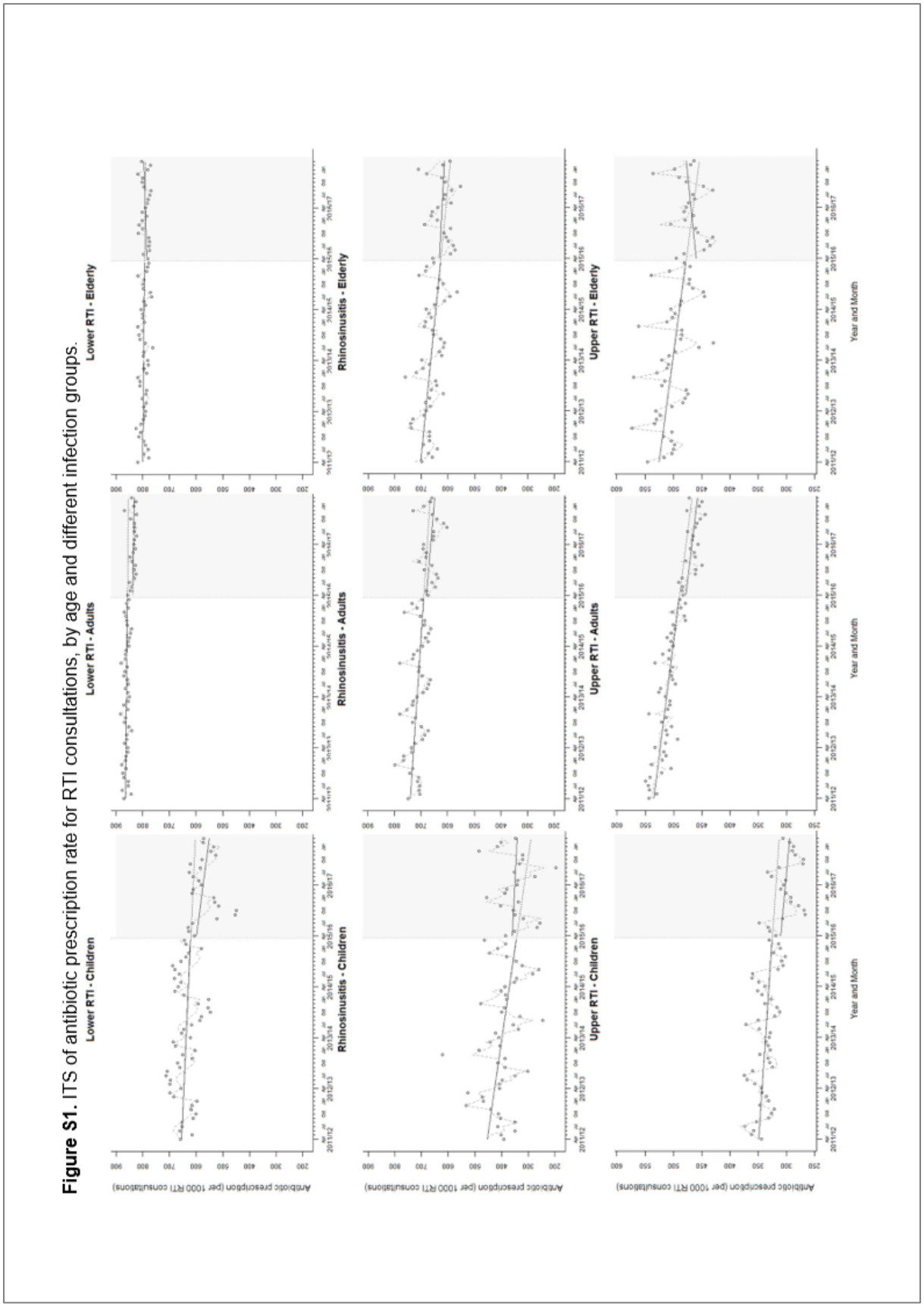


Figure S1. ITS of antibiotic prescription rate for RTI consultations, by age and different infection groups.

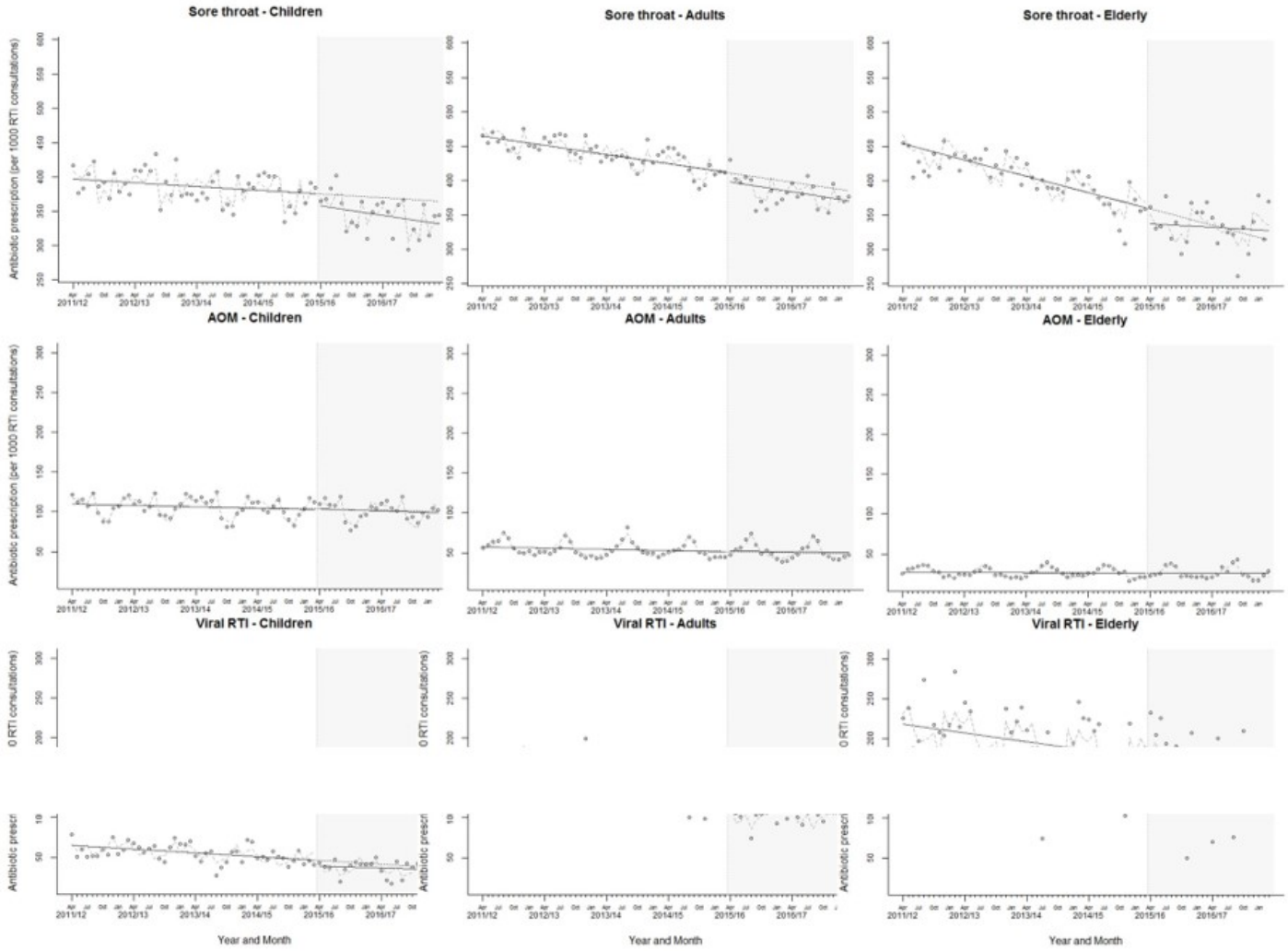

Sore throat - Children
Sore throat - Adults
Sore throat - Elderly
AOM - Children
AOM - Adults
AOM - Elderly
Viral RTI - Children
Viral RTI - Adults
Viral RTI - Elderly
Antibiotic prescription (per 1000 RTI consultations)
Year and Month

Table S2. Related findings from the ITS analysis, by age and infection group

RTI group		Estimate of intercept (*p*-value)	Pre-QP trend (*p*-value)	Change in level (*p*-value)	Change in post-QP trend (*p*-value)	Absolute change post 12 months	Relative change post 12 months (%)	Absolute change post 24 months	Relative change post 24 months (%)
Acute Otitis Media	Total	65.80 (<0.0001)	-0.11 (0.0126)	-0.36 (0.8603)	-0.02 (0.8827)	0.58	1	0.81	1
	Children	116.87 (<0.0001)	-0.13 (0.0794)	-0.38 (0.9137)	-0.08 (0.7215)	-0.56	-1	-1.50	-1
	Adult	52.89 (<0.0001)	-0.12 (0.0586)	0.87 (0.7459)	0.05 (0.7875)	1.44	3	2.01	5
	Elderly	23.58 (<0.0001)	-0.01 (0.6168)	-0.51 (0.7532)	0.03 (0.7547)	-0.15	-1	0.22	1
Rhinosinusitis	Total	729.26 (<0.0001)	-0.62 (0.0002)	-12.71 (0.0553)	-0.47 (0.3091)	-6.36	-1	-5.91	-1
	Children	455.68 (<0.0001)	-2.30 (<0.0001)	16.61 (0.0862)	1.47 (0.0162)	34.27	9	51.92	15
	Adult	745.57 (<0.0001)	-1.05 (<0.0001)	-9.35 (0.0470)	-0.287 (0.2993)	-12.80	-2	-16.24	-2
	Elderly	724.19 (<0.0001)	-1.56 (<0.0001)	3.79 (0.1265)	0.73 (0.0001)	12.57	2	21.36	4
Sore throat	Total	462.08 (<0.0001)	-1.04 (<0.0001)	-13.75 (0.0869)	-0.07 (0.9028)	-14.54	-4	-15.33	-4
	Children	408.67 (<0.0001)	-0.46 (0.0461)	-15.81 (0.1406)	-0.7239 (0.2760)	-24.49	-7	-33.18	-9
	Adult	478.78 (<0.0001)	-1.11 (<0.0001)	-13.13 (0.1197)	-0.07 (0.8957)	-14.00	-4	-14.86	-4
	Elderly	468.67 (<0.0001)	-1.97 (<0.0001)	-23.26 (0.0091)	1.55 (0.0044)	-4.67	-1	13.92	4
Upper RTI	Total	474.19 (<0.0001)	-0.76 (<0.0001)	-13.21 (0.0192)	0.28 (0.4297)	-9.88	-2	-6.55	-2
	Children	351.79 (<0.0001)	-0.51 (0.0009)	-14.82 (0.0280)	-0.17 (0.6860)	-16.90	-5	-18.98	-6
	Adult	539.41 (<0.0001)	-0.95 (<0.0001)	-11.50 (0.1243)	0.05 (0.9113)	-10.88	-2	-10.25	-2
	Elderly	544.54 (<0.0001)	-1.02 (<0.0001)	-18.42 (<0.0001)	1.75 (<0.0001)	2.58	1	23.57	5
Lower RTI	Total	811.38 (<0.0001)	-0.23 (0.0461)	-24.11 (0.0002)	0.28 (0.4352)	-20.74	-3	-17.38	-2
	Children	661.69 (<0.0001)	-0.71 (0.4364)	-19.42 (0.5117)	-1.42 (0.5798)	-36.47	-6	-53.53	-8
	Adult	864.43 (<0.0001)	-0.14 (<0.0001)	-19.16 (<0.0001)	0.16 (0.0800)	-21.12	-2	-23.10	-3
	Elderly	799.52 (<0.0001)	-0.14 (<0.0001)	-8.34 (<0.0001)	0.60 (<0.0001)	-1.13	0	6.09	1
Viral respiratory infection	Total	139.93 (<0.0001)	-0.70 (<0.0001)	-8.36 (0.2217)	0.39 (0.3565)	-3.72	-4	0.92	1
	Children	66.59 (<0.0001)	-0.38 (<0.0001)	-8.11 (0.0036)	0.24 (0.1496)	-5.29	-11	-2.47	-5
	Adult	178.60 (<0.0001)	-0.89 (<0.0001)	-16.32 (0.0002)	0.89 (0.0006)	-5.69	-5	4.94	5
	Elderly	231.05 (<0.0001)	-0.92 (0.0293)	-1.28 (0.9508)	-0.43 (0.7285)	-6.44	-4	-11.61	-7

Clinical Infectious Diseases

MAJOR ARTICLE

An Assessment of Potential Unintended Consequences Following a National Antimicrobial Stewardship Program in England: An Interrupted Time Series Analysis

Violeta Balinskaite,[1] Sabine Bou-Antoun,[2,3] Alan P. Johnson,[3,4] Alison Holmes,[2] and Paul Aylin[1,2,3]

[1]Dr Foster Unit, Department of Primary Care and Public Health, [2]Department of Primary Care and Public Health, and [3]Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, National Institute for Health Research, Imperial College London, and [4]National Infection Service, Public Health England, London, United Kingdom

(See the Major Article by Balinskaite et al on pages 227–32.)

Background. The "Quality Premium" (QP) introduced in England in 2015 aimed to financially reward local healthcare commissioners for targeted reductions in primary care antibiotic prescribing. We aimed to evaluate possible unintended clinical outcomes related to this QP.

Methods. Using Clinical Practice Research Datalink and Hospital Episode Statistics datasets, we examined general practitioner (GP) consultations (visits) and emergency hospital admissions related to a series of predefined conditions of unintended consequences of reduced prescribing. Monthly age- and sex-standardized rates were calculated using a direct method of standardization. We used segmented regression analysis of interrupted time series to evaluate the impact of the QP on seasonally adjusted outcome rates.

Results. We identified 27 334 GP consultations and >5 million emergency hospital admissions with predefined conditions. There was no evidence that the QP was associated with changes in GP consultation and hospital admission rates for the selected conditions combined. However, when each condition was considered separately, a significant increase in hospital admission rates was noted for quinsy, and significant decreases were seen for hospital-acquired pneumonia, scarlet fever, pyelonephritis, and complicated urinary tract conditions. A significant decrease in GP consultation rates was estimated for empyema and scarlet fever. No significant changes were observed for other conditions.

Conclusions. Findings from this study show that overall there was no significant association between the intervention and unintended clinical consequences, with the exception of a few specific conditions, most of which could be explained through other parallel policy changes or should be interpreted with caution due to small numbers.

Keywords. antimicrobial stewardship programs; antibiotic prescribing; unintended consequences; primary and secondary care; interrupted time series.

Antimicrobial resistance is a serious public health problem threatening to undermine modern medicine [1]. Prescribing and consumption of antibiotics is a key driver of resistance and there have been a number of antimicrobial stewardship programs (pay-for-performance, educational, audits, and guidelines) implemented in different countries with the intention of reducing inappropriate antimicrobial prescribing [2–10].

In the United Kingdom since the late 1990s, there have been various seasonal campaigns to reduce antibiotic prescribing [11]. However, the number of antimicrobial items dispensed over the period 2002–2012 increased by 17.1% [12]. In England, delivery of healthcare was reorganized in 2012, with the formation of Clinical Commissioning Groups (CCGs), which are clinically led statutory bodies responsible for the planning and commissioning of healthcare services for their local area. In 2015, a "Quality Premium" (QP) was published which aimed to financially reward CCGs for reducing unnecessary antibiotic prescribing in primary care [13]. We have already demonstrated that this intervention was associated with a significant decrease in all antibiotic items prescribed and in broad-spectrum antibiotic items prescribed (V. Balinskaite et al, unpublished data).

In this study, we established a method of surveillance of unintended consequences resulting from measures to reduce antibiotic prescribing. We hypothesized that the reduction in antibiotic prescribing following the introduction of the QP might increase the number of general practitioner (GP) consultations and hospital admissions associated with complications arising from predefined infections that may have been untreated, and we aimed to assess any such effect using interrupted time series (ITS) analysis.

METHODS

Study Design and Setting

We defined a range of conditions based on the hypothesis that the initial uncomplicated presentation in primary care might be thought to be self-limiting and therefore not treated with

Received 9 May 2018; editorial decision 20 September 2018; accepted 15 October 2018; published online October 18, 2018.

Correspondence: V. Balinskaite, Dr Foster Unit, School of Public Health, Imperial College London, 3 Dorset Rise, London EC4Y 8EN, UK (v.balinskaite@imperial.ac.uk).

Clinical Infectious Diseases® 2019;69(2):233–42

DOI: 10.1093/cid/ciy904

antibiotics. These cases may progress to these more severe conditions [14]. A list of Read codes (the standard clinical terminology system used in general practice in the United Kingdom) and *International Classification of Diseases, 10th Revision* (*ICD-10*) codes were compiled following a systematic search of the Read codes and Read terms in the Clinical Practice Research Datalink (CPRD) code browser, a search of the published literature on the CPRD website, and a short literature review, respectively. The finalized codes for both data sources were independently reviewed by an academic GP (Supplementary Tables 1–2). We selected diagnoses related to complications of both respiratory tract infection (community-acquired pneumonia [CAP], hospital-acquired pneumonia [HAP], mastoiditis, quinsy [peritonsillar abscess], meningitis, brain abscess, empyema, scarlet fever, and rheumatic fever) and urinary tract infection (pyelonephritis). We also selected specific clinical syndromes that may arise from an initial uncomplicated infection including complicated intra-abdominal infection (cIAI), complicated skin and skin structure infection (cSSSI), complicated urinary tract infection (cUTI), and sepsis.

Data Sources

We used datasets from the CPRD and Hospital Episode Statistics (HES). The CPRD is an administrative database of computerized medical records from a representative sample (~7%) of GPs across the United Kingdom [15–17]. It includes records of clinical events (medical diagnosis), referrals to specialists and secondary care settings, prescriptions issued in primary care, records of immunizations and vaccinations, diagnostic testing, and lifestyle-related information (eg, smoking and alcohol status). We used a standardized hierarchical classification system of Read codes to identify patients who had a recorded diagnosis, symptom, or process of care in the CPRD dataset related to the conditions of interest. CPRD flag GP practices and patients as having acceptable data where data has been verified and meets required CPRD data quality criteria. For this analysis, we included data from "up to standard" GP practices in England and patients who had been flagged as having acceptable records [17]. We extracted data covering the period April 2010 to December 2016, comprising 5 years before the QP was implemented and 21 months post-QP (being the most recent data available at the time of analysis).

HES is an administrative database that includes information on all inpatients admitted to English National Health Service (NHS) hospitals. Each record contains data on patients' demographics (eg, sex, age, and ethnicity), the episode of care (eg, trust name, date of admission), and clinical information. Diagnoses were recorded in HES using the *ICD-10*. Each patient episode was linked within a "spell" (admission to one provider) and spells were linked into "superspells," combining any interhospital transfers. We examined 7 years and 5 months of HES data (April 2010–August 2017): 5 years before the QP guidance was implemented and 29 months post-QP.

Intervention

"The Quality Premium: 2015/16 Guidance for CCGs" was published in April 2015 with the intention of rewarding CCGs in England for improvements in the quality of the services that they commission [13, 18, 19]. One of the measures was intended to improve antibiotic prescribing in primary care. We have shown a significant 8.2% decrease in all antibiotic items prescribed and a significant 18.9% decrease in broad-spectrum antibiotic items prescribed, associated with the introduction of the QP (V. Balinskaite et al, unpublished data).

Outcomes

We examined GP consultations rates for each of our predefined diagnosis groups before and after the introduction of the QP.

The main outcome of interest in secondary care was hospital admissions; these data were extracted based on *ICD-10* codes for our prespecified condition in the primary diagnosis field. The secondary outcomes were 30-day in-hospital mortality rates, 28-day emergency readmission rates, and long inpatient stay rates (long inpatient stay was defined as above the upper quartile of the length of stay for all years combined) related to the clinical condition syndromes (CAP, cIAI, cSSSI, cUTI, sepsis).

Statistical Analyses

We calculated monthly age- and sex-standardized rates and 95% confidence intervals (CIs) with 6 age bands (0–14, 15–44, 45–64, 65–74, 75–84, and ≥85 years) using the direct method of standardization [20]. For primary care consultations, we used monthly age- and sex-standardized GP consultation rates per million person-months for all conditions as a whole group, and individually, using age- and sex-specific denominators based on patients registered with CPRD practices during the same time period. For secondary care, we used monthly age- and sex-standardized admission rates per million population for all conditions combined, and separately, using midyear population estimates from the Office for National Statistics and the 2001 census as the standard population. Age- and sex-observed rates per 1000 admissions for other outcomes (7-day in-hospital mortality, 28-day emergency readmission, and long inpatient stay) were calculated using the number of hospital admissions as a denominator.

We used segmented regression analysis of ITS data to evaluate the impact of the QP on seasonally adjusted outcome rates (V. Balinskaite et al, unpublished data).

It is well known that age is the risk factor for mastoiditis, meningitis, and scarlet fever, and is more common among children. We performed a subgroup analysis for mastoiditis, meningitis, rheumatic fever, and scarlet fever for children aged 0–14 years. As a control group, we analyzed hospital admissions for diabetes and dementia (excluding those with a mention of condition), given that introduction of the 2015–2016 QP should have had no effect on these diseases.

In April 2017, new clinical coding standards were implemented, which recommended recording sepsis if present in the primary diagnosis [21]. We hypothesised this would dramatically increase the number of hospital admissions related to sepsis. Therefore, a sensitivity analysis was conducted for only 24 months after the intervention period, excluding data from April 2017.

Additional analysis for some of the rarer conditions (mastoiditis, brain abscess, and scarlet fever) was carried out by aggregating months into quarters. This allowed a sufficient number of cases per time point, to achieve more robust estimates of change.

All statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Ethical Considerations

The principal investigator has approval from the Secretary of State and the Health Research Authority under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to hold confidential data and analyze them for research purposes (Confidentiality Advisory Group [CAG] reference number 15/CAG/0005). The authors have the approval to use the data for research and measuring quality of delivery of healthcare from the London-South East Ethics Committee (reference number 15/LO/0824). The research protocol for the use of CPRD was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (protocol number 16_129R).

RESULTS

Between April 2010 and December 2016, we identified 27 334 GP consultations with our selected diagnosis groups. More than 34% of all consultations were related to CAP (34.4%), followed by pyelonephritis (24.7%) and scarlet fever (19.5%). More than half of the population was aged ≤64 years (73.9%) and female (62.0%) (Table 1; Supplementary Table 3). Scarlet fever was most common (83.4%) in children aged 0–14 years. A clear seasonal pattern was observed for CAP and scarlet fever. The seasonal pattern was also seen for all selected conditions combined,

Table 1. Total Numbers and Proportion of General Practitioner Consultations and Emergency Hospital Admissions in England by Age, Sex, and Infection Group

		Age, y						Sex
Conditions	Total	0–14	15–44	45–64	65–74	75–84	≥85	Female
Primary care (CPRD)								
All infections	27 334 (100)	5982 (21.9)	8693 (31.8)	5524 (20.2)	2404 (8.8)	2358 (8.6)	2373 (8.7)	16 956 (62.0)
CAP	9391 (34.4)	559 (6.0)	1492 (15.9)	2096 (22.3)	1360 (14.5)	1735 (18.5)	2149 (22.9)	4987 (53.1)
Mastoiditis	3479 (12.7)	609 (17.5)	1113 (32.0)	986 (28.3)	398 (11.4)	271 (7.8)	102 (2.9)	2113 (60.7)
Quinsy	1968 (7.3)	140 (7.1)	1444 (73.4)	307 (15.6)	55 (2.8)	16 (0.8)	6 (0.3)	957 (48.6)
Meningitis/brain abscess	186 (0.7)	46 (24.7)	61 (32.8)	45 (24.2)	17 (9.1)	11 (5.9)	6 (3.2)	103 (55.4)
Empyema	208 (0.8)	11 (5.3)	54 (26.0)	65 (31.3)	31 (14.9)	29 (13.9)	18 (8.7)	67 (32.2)
Scarlet fever	5336 (19.5)	4449 (83.4)	634 (11.9)	170 (3.2)	46 (0.9)	28 (0.5)	9 (0.2)	2828 (53.0)
Pyelonephritis	6738 (24.7)	165 (2.4)	3888 (57.7)	1849 (27.4)	493 (7.3)	263 (3.9)	80 (1.2)	5889 (87.4)
Secondary care (HES)								
All infections	5 103 733 (100)	352 091 (6.9)	1 037 852 (20.3)	936 776 (18.4)	735 706 (14.4)	1 045 926 (20.5)	995 382 (19.5)	2 690 007 (52.7)
CAP	1 419 093 (27.8)	77 270 (5.4)	101 179 (7.1)	210 837 (14.9)	249 751 (17.6)	389 352 (27.4)	390 704 (27.5)	701 381 (49.4)
HAP	178 911 (3.5)	4835 (2.7)	9211 (5.1)	26 767 (15.0)	32 816 (18.3)	51 888 (29.0)	53 394 (29.8)	86 577 (48.4)
Mastoiditis	5341 (0.1)	3343 (62.6)	1036 (19.4)	508 (9.5)	199 (3.7)	160 (3.0)	95 (1.8)	2487 (46.6)
Quinsy	55 835 (1.1)	2155 (3.9)	44 250 (79.3)	7903 (14.2)	1065 (1.9)	366 (0.7)	96 (0.2)	23 684 (42.4)
Meningitis	13 690 (0.3)	5646 (41.2)	3941 (28.8)	2447 (17.9)	960 (7.0)	523 (3.8)	173 (1.3)	6840 (50.0)
Brain abscess	3265 (0.1)	424 (13.0)	904 (27.7)	1118 (34.2)	483 (14.8)	263 (8.1)	73 (2.2)	1152 (35.3)
Empyema	9772 (0.2)	705 (7.2)	1719 (17.6)	3118 (31.9)	2075 (21.2)	1540 (15.8)	615 (6.3)	2974 (30.4)
Scarlet fever	5300 (0.1)	5118 (96.6)	163 (3.1)	16 (0.3)	1 (<0.1)	2 (<0.1)	0 (0.0)	2439 (46.0)
Rheumatic fever	325 (<0.1)	154 (47.4)	77 (23.7)	44 (13.5)	18 (5.5)	25 (7.7)	7 (2.2)	169 (52.0)
Pyelonephritis	170 297 (3.3)	8511 (5.0)	100 324 (58.9)	36 330 (21.3)	13 132 (7.7)	8868 (5.2)	3132 (1.8)	142 639 (83.8)
cIAI	300 948 (5.9)	21 939 (7.3)	124 113 (41.2)	85 462 (28.4)	32 934 (10.9)	24 990 (8.3)	11 510 (3.8)	126 372 (42.0)
cSSSI	1 100 167 (21.6)	85 983 (7.8)	345 678 (31.4)	286 266 (26.0)	143 278 (13.0)	141 082 (12.8)	97 880 (8.9)	525 791 (47.8)
cUTI	1 432 424 (28.1)	103 669 (7.2)	269 574 (18.8)	190 998 (13.3)	176 269 (12.3)	331 127 (23.1)	360 787 (25.2)	863 122 (60.3)
Sepsis	408 365 (8.0)	32 339 (7.9)	35 683 (8.7)	84 962 (20.8)	82 725 (20.3)	95 740 (23.4)	76 916 (18.8)	204 380 (50.0)
Diabetes	243 322	33 130 (13.6)	104 646 (43.0)	52 381 (21.5)	21 015 (8.6)	22 245 (9.1)	9905 (4.1)	115 216 (47.4)
Dementia	88 363	5 (<0.1)	102 (0.1)	2294 (2.6)	10 578 (12.0)	36 488 (41.3)	38 896 (44.0)	51 586 (58.4)

Data are presented as No. (%).

Abbreviations: CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infection; CPRD, Clinical Practice Research Datalink; cSSSI, complicated skin and skin structure infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HES, Hospital Episode Statistics.

though this overall pattern may be driven by CAP and scarlet fever (Supplementary Table 4). The segmented regression model showed that the standardized GP consultation rates, combining the change in level and the change in slope, did not change significantly over the study period for all the selected conditions combined (change in level: −3.623, $P = .64$; change in slope: 0.327, $P = .86$) (Table 2; Figure 1). Although there was no significant change in level and in slope in the age- and sex-standardized GP consultation rates, looking at each condition separately, a significant decrease in relative change was estimated for empyema by −86.8% (95% confidence interval [CI], −127.6% to −46.1%) and scarlet fever by −26.7% (95% CI, −48.6% to −4.8%), indicating approximately 1219 and 13 736 fewer GP consultations during the 21-month period after the QP was introduced, respectively. No significant change was observed for other conditions.

We identified 5 103 733 emergency hospital admissions using our predefined condition *ICD-10* codes in the primary diagnosis between April 2010 and August 2017. Nearly 30% of all admissions were cUTIs (28.1%), followed by CAP (27.8%) and cSSSIs (21.6%). More than half of the population was 65 years or older (54.4%) and female (52.7%) (Supplementary Tables 3 and 4). Mastoiditis, meningitis, scarlet fever, and rheumatic fever were more common in children aged 0–14 years. The seasonal pattern was present in all conditions, except for brain abscess and rheumatic fever (Supplementary Table 5). The age- and sex-standardized hospital admission rates for CAP and HAP were highest during the winter period, whereas standardized hospital admission rates for pyelonephritis reached a peak in late summer/early autumn. After the QP had been implemented, the segmented regression model showed no significant drop in level for all conditions combined; however, a significant change in slope (change in trend) was obtained. There was no statistically significant relative change (0.7% [95% CI, −3.9% to 5.4%]), representing 13 623 (95% CI, −70 052 to 97 282) more hospital admissions during the 29 postintervention months compared with the expected number of hospital admissions based on the trend in the preintervention

Table 2. Segmented Regression Analysis for Antibiotic Prescribing Measures (April 2013–February 2017), Age- and Sex-standardized Rates for General Practitioner Consultations Rated per Million Person-Months (April 2010–December 2016), and Age- and Sex-standardized Rates for Emergency Hospital Admissions per Million Population in England (April 2010–September 2017)

Outcome	Constant	Preintervention Trend (*P* Value)	Change in Level (*P* Value)	Postintervention Trend (*P* Value)	Absolute Change in Outcome per Month During Postintervention Period (95% CI)	Relative Change by the End of the Study, % (95% CI)
Primary care (CPRD)						
All infections	98.749	0.425 (<.01)	−3.623 (.64)	0.327 (.86)	−5.68 (−23.23 to 11.86)	−4.3 (−17.5 to 8.9)
CAP	38.676	−0.099 (<.01)	1.011 (.68)	0.031 (.46)	3.74 (−1.69 to 9.17)	12.2 (−6.5 to 30.9)
Mastoiditis	17.149	−0.092 (<.01)	0.172 (.93)	0.157 (.09)	5.39 (.88 to 9.92)	55.4 (−6.0 to 116.8)
Quinsy	8.581	0.000 (.99)	−0.726 (.55)	−0.028 (.75)	−1.31 (−4.02 to 1.39)	−15.3 (−45.2 to 14.6)
Meningitis/brain abscess	0.833	−0.003 (.44)	−0.002 (.99)	0.024 (.15)	0.57 (−.01 to 1.15)	96.9 (−53.5 to 247.5)
Empyema	0.689	0.006 (.17)	−0.320 (.29)	−0.027 (.12)	−1.01 (−1.66 to −.36)	−86.8 (−127.6 to −46.1)
Scarlet fever	11.919	0.379 (<.01)	−1.687 (.71)	−0.083 (.16)	−11.38 (−21.62 to −1.14)	−26.7 (−48.6 to −4.8)
Pyelonephritis	21.205	0.206 (<.01)	−1.466 (.63)	0.239 (.88)	−0.78 (−7.59 to 6.03)	−2.1 (−20.2 to 16.2)
Secondary care (HES)						
All infections	814.009	3.988 (<.01)	−10.362 (.61)	4.639 (.55)	8.51 (−43.76 to 60.77)	0.7 (−3.9 to 5.4)
CAP	212.169	1.315 (<.01)	9.739 (.54)	0.124 (.19)	−24.80 (−67.81 to 18.21)	−7.5 (−20.9 to 5.8)
HAP	19.354	0.329 (<.01)	−0.013 (.99)	0.175 (.06)	−4.49 (−8.36 to −.62)	−9.2 (−17.1 to −1.3)
Mastoiditis	1.005	0.001 (.44)	0.155 (.13)	0.006 (.41)	0.29 (.00 to .55)	25.4 (−2.4 to 53.2)
Quinsy	9.600	0.046 (<.01)	−0.388 (.19)	0.098 (<.01)	1.13 (.41 to 1.86)	8.3 (2.7 to 13.9)
Meningitis	2.721	0.004 (.10)	0.191 (.20)	−0.014 (.02)	−0.33 (−.71 to .04)	−10.8 (−22.4 to .8)
Brain abscess	0.623	0.001 (.24)	−0.028 (.62)	0.000 (.63)	−0.07 (−.20 to .07)	−9.3 (−27.3 to 8.6)
Empyema	1.813	0.001 (.42)	0.103 (.32)	0.001 (.92)	0.09 (−.17 to .34)	4.5 (−9.1 to 18.2)
Scarlet fever	0.496	0.016 (<.01)	0.198 (.20)	−0.009 (<.01)	−0.53 (−.92 to −.14)	−28.0 (−45.6 to −10.5)
Rheumatic fever	0.055	0.0002 (.35)	0.025 (.11)	−0.001 (.23)	−0.003 (−.04 to .04)	−3.5 (−53.0 to 46.0)
Pyelonephritis	25.170	0.243 (<.01)	1.188 (.19)	0.006 (<.01)	−5.68 (−8.01 to −3.36)	−12.2 (−16.9 to −7.4)
cIAI	56.310	0.094 (<.01)	0.038 (.96)	0.164 (.12)	2.05 (−.09 to 4.20)	3.2 (−.3 to 6.7)
cSSSI	203.003	0.322 (<.01)	2.398 (.58)	0.469 (.56)	6.65 (−5.35 to 18.65)	2.9 (−2.8 to 8.5)
cUTI	248.265	0.928 (<.01)	0.830 (.89)	−1.654 (<.01)	−74.07 (−109.11 to −39.03)	−22.4 (−32.3 to −12.5)
Sepsis	35.956	0.542 (.19)	−10.231 (.44)	4.735 (<.01)	111.36 (54.83 to 167.88)	132.2 (−14.0 to 278.4)
Controls (excluding admissions with a mention of condition)						
Diabetes	50.155	−0.019 (.17)	1.707 (.04)	0.021 (.92)	2.87 (.76 to 4.98)	5.9 (1.3 to 10.5)
Dementia	18.639	−0.041 (<.01)	0.935 (.22)	−0.142 (.02)	−1.99 (−3.97 to −.01)	−13.3 (−26.0 to −.5)

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; cIAI, complicated intra-abdominal infection; CPRD, Clinical Practice Research Datalink; cSSSI, complicated skin and skin structure infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HES, Hospital Episode Statistics.

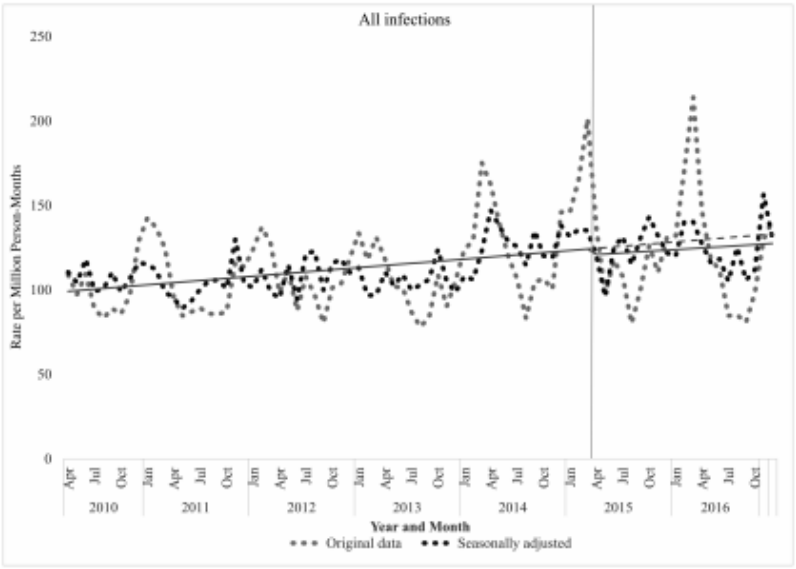


Figure 1. Segmented regression analysis for age- and sex-standardized general practitioner consultation rates per million person-months for all conditions combined. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimates without intervention. Implementation of the Quality Premium (represented by a vertical gray line) occurred in April 2015.

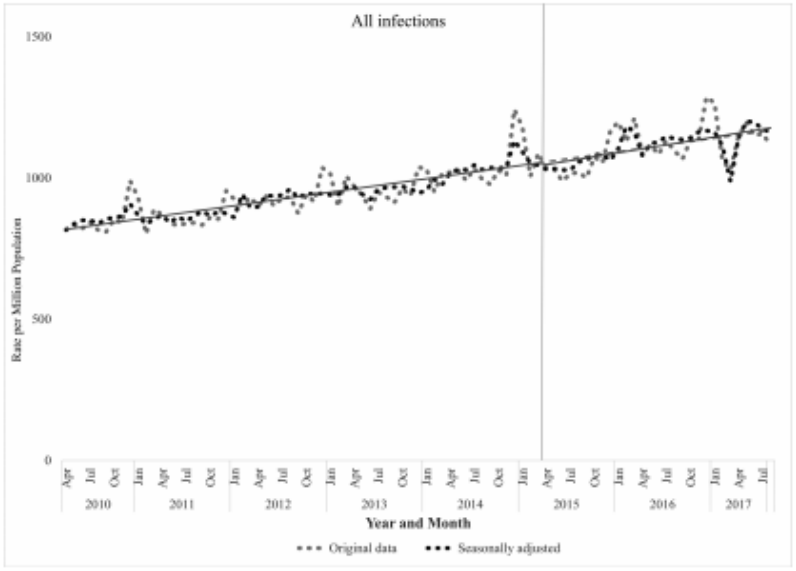


Figure 2. Segmented regression analysis for age- and sex-standardized emergency hospital admission rates per million population for all conditions combined. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimates without intervention. Implementation of the Quality Premium (represented by a vertical gray line) occurred in April 2015.

period (Table 2; Figure 2). There was no significant change in standardized hospital admission rates for CAP, mastoiditis, meningitis, empyema, rheumatic fever, cIAIs, cSSSIs, and sepsis. The standardized hospital admission rates significantly increased for quinsy by 8.3% (95% CI, 2.7%–13.9%). However, a significant decrease in standardized hospital admission rates was observed for HAP by 9.2% (95% CI, −17.1% to −1.3%), scarlet fever by 28.0% (95% CI, −45.6% to −10.5%), pyelonephritis by 12.2% (95% CI −16.9% to −7.4%), and cUTIs by 22.4% (95% CI, −32.3% to −12.5%) (Table 2; Figures 3–5; Supplementary Figures 1–4). In our subgroup analysis, we found a significant decrease in age- and sex-standardized hospital admission rates for children aged 0–14 years for meningitis (−21.0% [95% CI, −39.9% to −9.1%]) and scarlet fever (−22.9% [95% CI, −44.5% to −1.3%]), and no significant change for mastoiditis and rheumatic fever (Supplementary Table 5). Furthermore, a significant change was estimated for the control group.

During the same study period, there was no significant change in the age- and sex-standardized 30-day in-hospital mortality rates for CAP, cIAI, cSSSI, cUTI, and sepsis (Supplementary Table 6). A significant increase in standardized 28-day emergency readmission rates was estimated for cSSSIs. The age- and sex-standardized long inpatient stay significantly increased for sepsis; though there was a significant decrease in other clinical condition syndromes.

Sensitivity Analysis

For the sensitivity analysis, we also performed a second segmented regression analysis including only 24 months after the intervention (Supplementary Table 7). This analysis showed no significant change in standardized hospital admission rates for HAP and a significant increase for mastoiditis, cIAIs, and sepsis. For the remaining conditions, similar results were found compared with the 29-month analysis after the intervention. An additional analysis of rare conditions by quarter showed a significant increase in standardized hospital admission rates for mastoiditis and a significant decrease for scarlet fever; however, no significant changes were observed for brain abscess (Supplementary Table 8).

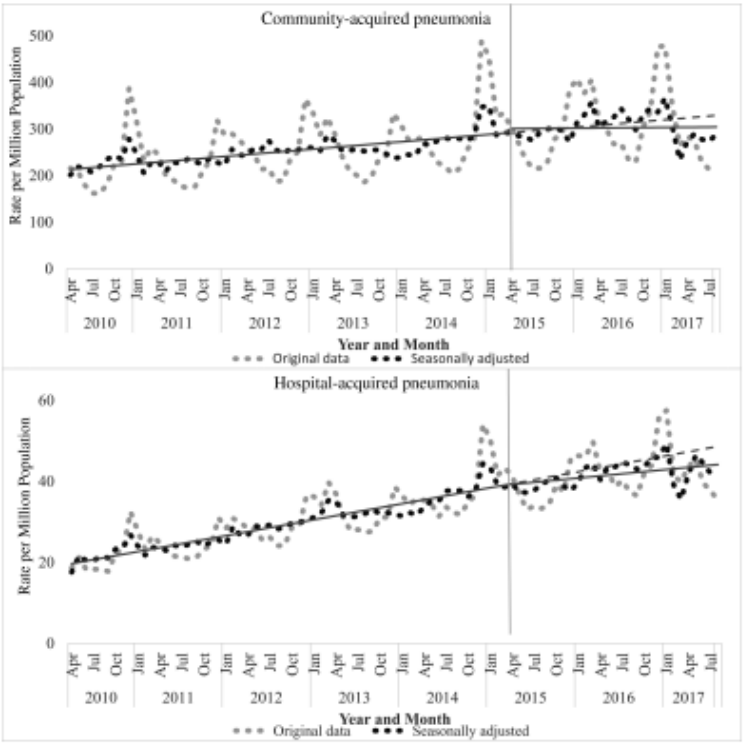


Figure 3. Segmented regression analysis for age- and sex-standardized emergency hospital admission rates per million population for community- and hospital-acquired pneumonia. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimates without intervention. Implementation of the Quality Premium (represented by a vertical gray line) occurred in April 2015.

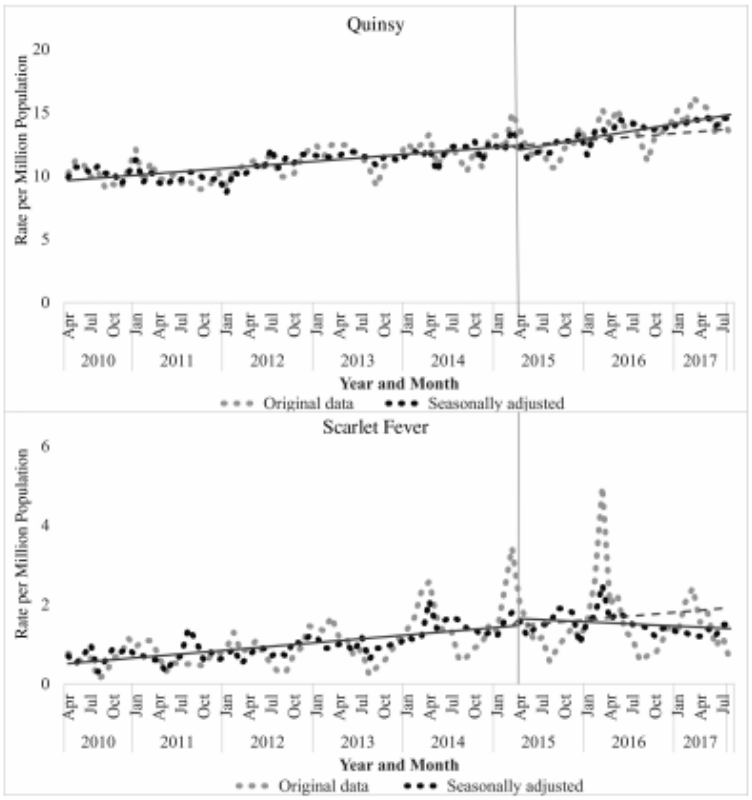


Figure 4. Segmented regression analysis for age- and sex-standardized emergency hospital admission rates per million population for quinsy and scarlet fever. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimates without intervention. Implementation of the Quality Premium (represented by a vertical gray line) occurred in April 2015.

DISCUSSION

In our analysis, we found no significant association between the QP and GP consultation rates for all the selected conditions combined. No significant association was observed between the QP and hospital admission rates for all the selected conditions and complications combined.

Our study is the first to investigate the association between the QP and adverse clinical outcomes in primary and secondary care and, to our knowledge, the first study in the globe to evaluate the potential unintended consequences of a national antimicrobial stewardship initiative with a financial incentive. However, there are several studies that have looked at the association between antimicrobial stewardship programs with no financial initiatives (educational and guidelines) and adverse outcome, and found mixed results [6, 22, 23]. A study in Wales looked at the association between a multifaceted educational program (with no financial initiatives) and adverse outcome. The authors, using a practice-based randomized controlled trial (RCT), found no significant differences in reconsultation rates and hospital admissions for respiratory tract conditions between practices that received an educational program and control practices that provided usual care [6]. Our study included an analysis of the complications of respiratory tract conditions, and similar results were found. A recent retrospective study in Italy that investigated the impact of the Italian pediatric guidelines for the treatment of acute otitis media found no association between new guidelines and the number of cases of mastoiditis [22]. In addition, the authors did not find any changes in antibiotic prescribing after the guidelines were implemented. Furthermore, a descriptive statistic was used to determine associations. Using ITS analysis, we found no significant change in hospital admissions for mastoiditis for children aged 0–14 years. Another study in Scotland looked at the association between the antimicrobial stewardship program and

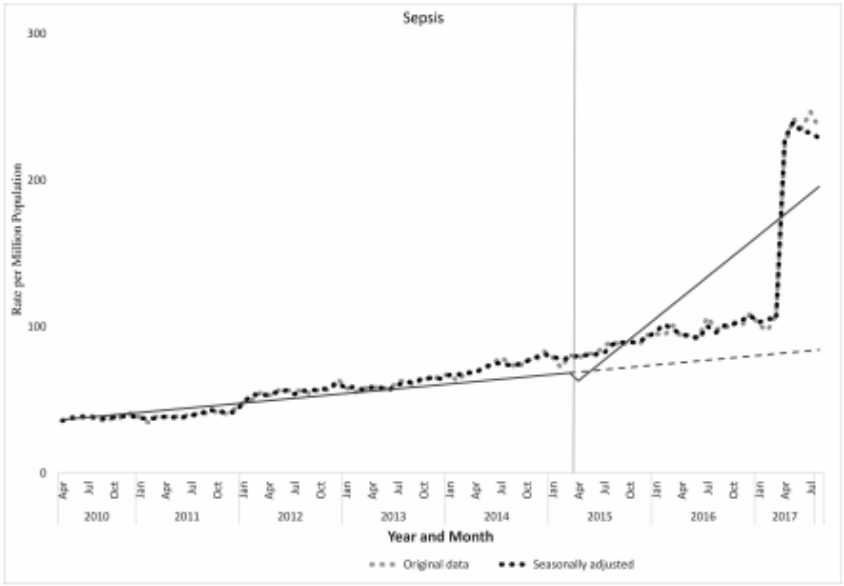


Figure 5. Segmented regression analysis for age- and sex-standardized emergency hospital admission rates per million population for sepsis. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimates without intervention. Implementation of the Quality Premium (represented by a vertical gray line) occurred in April 2015.

unintended harm resulting in hospital admissions for peritonsillar abscess, mastoiditis, and CAP [23]; the authors found no evidence that reduction in unnecessary antibiotic use has resulted in patients with serious respiratory tract conditions.

The main strength of this study is the use of a large and rich national administrative hospital and GP datasets. Another strength is the use of an ITS design to assess the impact of the QP. ITS is the strongest quasi-experimental research design and is very useful when an RCT is either not feasible or unethical. Segmented regression analysis is a useful statistical method that addresses important threats to internal validity by making multiple assessments of the outcome variable both before and after the intervention. It can estimate the size of the association at different time points, as well as changes in the trend of the association over time. Though there is a concern around HES data quality of the primary and secondary diagnosis and procedure fields, a recent systematic review of discharge coding accuracy in UK data found that primary diagnosis accuracy has improved since the introduction of Payment by Results in 2002 [24]. The review showed that the primary diagnosis accuracy improved significantly from 73.85% to 96.0% and concluded that routinely collected data are sufficiently robust. Furthermore, submission of HES records is mandatory and, in general, coverage is very high [25].

There are several limitations that need to be considered when interpreting the findings. First, a longer postintervention period for GP consultations would adequately include seasonal variation (minimum 24 time points after intervention) and might allow a sufficient number of observations per time point, by aggregating months into quarters (a minimum of 100 cases is desirable) [26]. However, fulfilling the latter condition for meningitis/brain abscess and empyema is not practical, even with a longer postintervention period, due to the small number of GP consultations per year. Furthermore, a postintervention period >24 months is needed for quinsy, in order to have a sufficient number of GP consultations per time point. Second, there have been multiple national and local interventions and change in management during the study period. CCGs started to manage tonsillectomy as an individual funding request, and according to summary reports on inpatient activities (from NHS Digital), there was a decrease in procedures related to "excision of tonsils" from 2015 to 2016. In other research, it has been shown that a decrease in the rate of tonsillectomy in England and Wales was associated with an increase in hospital admissions for tonsillitis [27, 28].

For sepsis, there was a parallel national intervention that was introduced (Commissioning for Quality and Innovation Guidance for 2015– 2016), which provided financial incentives for hospitals to undertake certain actions. Two new indicators were introduced relating to the identification and early treatment of sepsis. This raised the rate of screening for sepsis

among emergency departments from 52% to 80%. New clinical coding standards were implemented in April 2017, which recommended recording sepsis in the primary diagnosis if present [21]. This is likely to account for the jump in trend in the last few months of observation (Figure 5).

Finally, our study was not able to identify a causal relationship between the QP and hospital admissions rates. It is difficult and rarely possible to do RCTs to evaluate the impact of policy changes. However, observational studies based on ITS analyses are a valid approach.

CONCLUSIONS

In conclusion, we find no significant association between a national antimicrobial stewardship program and unintended clinical consequences in primary and secondary care, with the exception of a few specific conditions, most of which could be explained through other parallel policy changes or should be interpreted with caution due to small numbers. This observational study can never identify a causal relationship between the QP and possible unintended clinical outcomes; however, our findings can perhaps reassure patients, GPs, and policymakers that reducing unnecessary antibiotic prescriptions in primary care does not appear to be associated with an overall increase in unintended clinical outcomes. We believe these findings may also be of interest to other countries implementing similar stewardship programs. However, continued surveillance is necessary to monitor the effects of future national interventions to reduce antibiotic prescribing, and further work is required to examine whether specific groups of patients are more at risk of unintended consequences.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. V. B., A. P. J., A. H., and P. A. contributed to the original research proposal and helped refine the classification of outcomes used and the procedure groups for further analysis. S. B.-A. prepared the Independent Scientific Advisory Committee (ISAC) protocol for Clinical Practice Research Datalink (CPRD) and provided the initial CPRD Read code lists. V. B. carried out the analysis. V. B. and P. A. wrote the first draft, and all authors commented on subsequent drafts of the manuscript.

Acknowledgments. The authors thank Dr Benedict Hayhoe for his input into finalizing the Read code list, and Fran Husson and Tim Sims for their contribution toward the ISAC protocol.

Disclaimer. The views expressed in this article are those of the authors and do not necessarily represent the position of the funder. The findings achieved herein are solely the responsibility of the authors.

Financial support. This work was supported by the National Institute for Health Research (NIHR) Policy Research Programme (research to determine the impact of the national antimicrobial stewardship programs on clinical outcomes and patient safety and establish sustainable systems). The Dr Foster Unit is an academic unit in the Department of Primary Care and Public Health, within the School of Public Health, Imperial College London (ICL). The unit receives research funding from the NIHR and Dr Foster Intelligence, an independent health service research organization (a wholly owned subsidiary of Telstra). This work was by supported by the NIHR Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at ICL in partnership with Public Health England. The Dr Foster Unit at ICL is affiliated with the NIHR Imperial Patient Safety Translational Research Centre, which is a partnership between the Imperial College Healthcare NHS Trust and ICL. The Department of Primary Care and Public Health at ICL is grateful for support from the Northwest London NIHR Collaboration for Leadership in Applied Health Research and Care and the Imperial NIHR Biomedical Research Centre.

Potential conflicts of interest. A. H. is the director of NIHR HPRU in Healthcare Associated Infections and Antimicrobial Resistance and a professor at ICL; she also received an honorarium for presenting at the South African Antibiotic Stewardship Programme Annual Workshop, sponsored by Merck (MSD Hoddesdon). P. A. has received grants from Dr Foster (a wholly owned subsidiary of Telstra Health) and NIHR. V. B. has received grants from the UK Department of Health. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE form for disclosure of potential conflicts of interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. O'Neill J. Securing new drugs for future generations: the pipeline of antibiotics. Review on Antimicrobial Resistance. London: Wellcome Trust, **2015**.
2. Yip W, Powell-Jackson T, Chen W, et al. Capitation combined with pay-for-performance improves antibiotic prescribing practices in rural China. Health Aff **2014**; 33:502–10.
3. Mullen KJ, Frank RG, Rosenthal MB. Can you get what you pay for? Pay-for-performance and the quality of healthcare providers. Rand J Econ **2010**; 41:64–91.
4. Ellegård LM, Dietrichson J, Anell A. Can pay-for-performance to primary care providers stimulate appropriate use of antibiotics? Health Economics **2018**; 27:e39–54.
5. Bou-Antoun S, Costelloe C, Honeyford K, et al. Age-related decline in antibiotic prescribing for uncomplicated respiratory tract conditions in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis. J Antimicrob Chemother **2018**; 73:2883–92.
6. Butler CC, Simpson SA, Dunstan F, et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. BMJ **2012**; 344:d8173.
7. Gerber JS, Prasad PA, Fiks AG, et al. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. JAMA **2013**; 309:2345–52.
8. Hemkens LG, Saccilotto R, Reyes SL, et al. Personalized prescription feedback using routinely collected data to reduce antibiotic use in primary care: a randomized clinical trial. JAMA Intern Med **2017**; 177:176–83.
9. Mölstad S, Erntell M, Hanberger H, et al. Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. Lancet Infect Dis **2008**; 8:125–32.
10. van der Velden AW, Pijpers EJ, Kuyvenhoven MM, Tonkin-Crine SK, Little P, Verheij TJ. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. Br J Gen Pract **2012**; 62:e801–7.
11. Collier J, Foster J. Management of a restricted drugs policy in hospital: the first five years' experience. Lancet **1985**; 1:331–3.
12. National Health Service Digital. Prescriptions dispensed in the community, statistics for England: 2002–2012.
13. National Health Service England. Quality Premium: 2015/16 guidance for CCGs, 21 September 2015. Available at: https://www.england.nhs.uk/wp-content/uploads/2013/12/qual-prem-guid.pdf. Accessed 5 September 2016.
14. Gulliford MC, Moore MV, Little P, et al. Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care: cohort study using electronic health records. BMJ **2016**; 354:i3410.
15. Kousoulis AA, Rafi I, de Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. Br J Gen Pract **2015**; 65:54–5.
16. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. Pharmacotherapy **2003**; 23:686–9.

17. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol **2015**; 44:827–36.
18. Naylor C, Curry N, Holder H, et al. Clinical commissioning groups. Supporting improvement in general practice? The King's Fund 2013. Available at: https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/clinical-commissioning-groups-report-ings-fund-nuffield-jul13.pdf. Accessed 16 June 2018.
19. Li G, Hooper C, Papanikitas A, Hopkins S, Sharland M. The ethics of setting national antibiotic policies using financial incentives. Br J Gen Pract **2017**; 67:419–20.
20. Naing NN. Easy way to learn standardization: direct and indirect methods. Malays J Med Sci **2000**; 7:10–5.
21. National Health Service Digital. Coding clinic, March 2017. Available at: file:///C:/Users/vbalinsk/Desktop/Coding_Clinic_032017_V6.2.pdf. Accessed 25 January 2018.
22. Palma S, Rosafio C, Del Giovane C, et al. The impact of the Italian guidelines on antibiotic prescription practices for acute otitis media in a paediatric emergency setting. Ital J Pediatr **2015**; 41:37.
23. National Health Service, National Services Scotland Information Services Division. Measuring potential unintended consequences of reducing primary care antimicrobial prescribing using NHS Scotland's condition intelligence platform. Available at: http://www.isdscotland.org/Health-Topics/Health-and-Social-Community-Care/Condition-Intelligence-Platform/Communications/_docs/20162709_Poster_7b.pdf. Accessed 8 December 2017.
24. Burns EM, Rigby E, Mamidanna R, et al. Systematic review of discharge coding accuracy. J Public Health **2012**; 34:138–48.
25. Health and Social Care Information Centre. NHS hospital data and datasets: a consultation. **2013**.
26. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther **2002**; 27:299–309.
27. Mcleod R, Brahmabhatt P, Owens D. Tonsillectomy is not a procedure of limited value—the unseen costs of tonsillitis and quinsy on hospital bed consumption. Clin Otolaryngol **2017**; 42:573–7.
28. Al-Hussaini A, Owens D, Tomkinson A. Health costs and consequences: have UK national guidelines had any effect on tonsillectomy rates and hospital admissions for tonsillitis? Eur Arch Otorhinolaryngol **2013**; 270:1959–65.