

Antibiotic prescribing and resistance in primary care: implications for intervention

OLIVER VAN HECKE

St Hugh's College

A thesis submitted to the Division of Medical Sciences at the
University of Oxford for the Degree of
Doctor of Philosophy
Michaelmas Term 2017

Nuffield Department of Primary Care Health Sciences
University of Oxford



I dedicate this thesis to my parents.

Thank you for giving me the strength to deal with life's challenges to the best of my ability.

CONTENTS

ABSTRACT	7
ACKNOWLEDGEMENTS.....	11
CHAPTER 1 Introduction	13
CHAPTER 2 Current practices of antibiotic prescribing and antibiotic awareness campaigns in primary care.....	15
2.1 Introduction	15
2.2 Aims and objectives	15
2.3 Methods.....	15
2.4 Antibiotic prescribing in primary care	15
2.5 Appropriateness of antibiotics for respiratory tract infections.....	16
2.6 Antibiotic awareness campaigns	18
2.7 Public misconceptions about antibiotic resistance	21
2.8 Current evidence for antibiotic resistance in primary care.....	23
2.8.1 Antibiotic resistance	23
2.8.2 Why antibiotic resistance occurs.....	24
2.8.3 The link between antibiotic use and antibiotic resistance in the community	24
2.8.4 How quickly does antibiotic resistance develop?.....	26
2.8.5 The reversibility of antibiotic resistance	27
2.8.6 The evidence gaps	29
2.8.7 Better evidence to ensure long-term effectiveness of antibiotics	30
2.9 References	31
CHAPTER 3 Aims, objectives and structure of thesis	37
3.1 Aims and objectives	37
3.2 Overall structure of thesis and studies to address objectives	37

CHAPTER 4 The implications of antibiotic resistance for patients’ recovery from common infections in the community: a systematic review and meta-analysis 39

4.1	Introduction.....	39
4.2	Aims and objectives.....	39
4.3	Methods.....	39
4.3.1	Protocol and registration	39
4.3.2	Search strategy	40
4.3.3	Supplementary search	40
4.3.4	Inclusion criteria	41
4.3.5	Exclusion criteria	41
4.3.6	Selection procedure.....	42
4.3.7	Data extraction	42
4.3.8	Risk of bias assessment.....	43
4.3.9	Statistical analysis.....	43
4.4	Results.....	48
4.4.1	Study selection.....	48
4.4.2	Study characteristics	49
4.4.3	Primary outcome	51
4.4.4	Secondary outcomes	54
4.4.5	Subgroup analysis	56
4.4.6	Sensitivity analysis.....	56
4.5	Discussion.....	56
4.5.1	Main findings	56
4.5.2	Strengths and limitations.....	57
4.5.3	Conclusions.....	59
4.6	References.....	59

CHAPTER 5 The relationship between antibiotic exposure and antibiotic “response failure” in children presenting with acute respiratory tract infections in primary care: an observational cohort study 63

5.1	Introduction.....	63
-----	-------------------	----

5.1.1	Background and rationale.....	63
5.1.2	Antibiotic exposure in childhood and its consequences.....	64
5.1.3	Concept of “failure to respond” to antibiotics in primary care.....	65
5.1.4	Aim and Objectives.....	67
5.2	Methods.....	68
5.2.1	Protocol	68
5.2.2	The Clinical Practice Research Datalink (CPRD).....	68
5.2.3	Study population	69
5.2.4	Sample size calculation	70
5.2.5	Data management.....	71
5.2.6	Outcome	73
5.2.7	Descriptive analysis.....	74
5.2.8	Statistical analysis	74
5.3	Results	76
5.3.1	Primary Analysis	76
5.3.2	Secondary analysis	81
5.3.3	Sensitivity analyses	84
5.3.4	Subgroup analysis	85
5.4	Discussion	85
5.4.1	Main findings	85
5.4.2	Strengths and Limitations.....	85
5.4.3	Conclusion.....	88
5.5	References	88

CHAPTER 6 Parents’ perceptions of antibiotic use and antibiotic resistance (PAUSE): a qualitative interview study 93

6.1	Introduction	93
6.1.1	Parents’ experiences of managing their child’s illness.....	94
6.1.2	Parental concern about antibiotics and their potential effects	95
6.1.3	A bottom-up approach to improving antibiotic stewardship.....	97
6.2	Aims and objectives	100
6.2.1	Aim.....	100
6.2.2	Objectives.....	100
6.3	Methods.....	100

6.3.1	Study design and justification	100
6.3.2	Participants.....	101
6.3.3	Recruitment.....	102
6.3.4	Patient and public involvement (PPI)	104
6.3.5	Data collection	105
6.3.6	Data saturation	106
6.3.7	Researcher characteristics and reflexivity.....	108
6.3.8	Data analysis	110
6.3.9	Quality in qualitative research	113
6.3.10	Ethics.....	114
6.4	Results.....	114
6.4.1	Participant characteristics	114
6.4.2	Qualitative findings.....	117
	Theme 1: Parents' experiences of managing RTIs in their children	118
	Theme 2: Parents' experiences of consulting the GP for treatment.....	119
	Theme 3: Uncertainty about the risks of antibiotics and their use	122
	Theme 4: Parents' understanding of antibiotic resistance.....	126
	Theme 5: Perceived consequences of antibiotic resistance.....	128
	Theme 6: Ways to reduce antibiotic resistance in response to campaign materials.....	132
	Theme 7: Parents' reflections on current antibiotic awareness materials	133
	Theme 8: Social responsibility to inform parents about antibiotic resistance.....	135
6.5	Discussion	137
6.5.1	Summary of main findings.....	137
6.5.2	Strengths and limitations.....	138
6.5.3	Conclusions.....	141
6.6	References.....	141
CHAPTER 7	Discussion.....	147
7.1	Summary of main findings.....	147
7.2	Comparison with existing literature	148
7.2.1	The impact of antibiotic resistance on patient recovery from common infections in the community	148
7.2.2	The relationship between antibiotic exposure and clinical response failure in preschool children with acute respiratory tract infections	149

7.2.3	Parents' perceptions of antibiotic use and antibiotic resistance in the community	152
7.3	Implications of findings for clinical practice	155
7.4	Implications of findings for policy	158
7.5	Implications of findings for future research	159
7.6	Final reflections of thesis	161
7.7	Conclusions	162
7.8	References	163
APPENDICES.....		171
APPENDIX 1 – Search strategy of electronic databases for background literature review.....		171
APPENDIX 2 – Search strategy of electronic databases for systematic review and meta-analysis		173
APPENDIX 3 – Risk of bias assessment tool and coding criteria for included randomised controlled studies modelled on the Cochrane Collaboration's tool for assessing risk of bias in randomised trials		177
APPENDIX 4 – Risk of bias assessment tool and coding criteria for included observational studies based on CASP (Critical Appraisal Skills Programme) checklist for cohort studies.....		179
APPENDIX 5 – Diagnostic approach of significant bacterial infection in <i>E. coli</i> urinary tract infections.....		182
APPENDIX 6 – Diagnostic approach of significant bacterial infection in <i>S. pneumoniae</i> community-acquired pneumonia.....		183
APPENDIX 7 – Diagnostic approach of significant bacterial infection in <i>S. pneumoniae</i> acute otitis media		183
APPENDIX 8 – Unadjusted odds ratios for clinical response failure between antibiotic-resistant and antibiotic-sensitive Group A β -haemolytic streptococcus sore throat		184
APPENDIX 9 – Unadjusted odds ratios for clinical response failure between antibiotic-resistant and antibiotic-sensitive <i>S. pneumoniae</i> acute maxillary sinusitis		184
APPENDIX 10 – Unadjusted odds ratios for clinical response failure between antibiotic-resistant and antibiotic-sensitive <i>S. aureus</i> skin infection.....		185
APPENDIX 11 – Unadjusted odds ratios for “patient re-consultation” between antibiotic-resistant and antibiotic-sensitive <i>E. coli</i> urinary tract infections.....		186
APPENDIX 12 – Unadjusted odds ratios for “further antibiotic prescription” between antibiotic-resistant and antibiotic-sensitive infections.....		186
APPENDIX 13 – CPRD diagnostic codes for acute respiratory tract infections (RTI)		187
APPENDIX 14 – CPRD Product Codes for relevant antibiotics used in the treatment of acute “respiratory tract infections” as listed in the British National Formulary (BNF) for Children Chapter 5.1		192

APPENDIX 15 – Further details about covariates (extract from ISAC Protocol 16_162R)	246
APPENDIX 16 – Secondary analysis: relationship between RTI-associated antibiotic exposure in the 12 months prior to index consultation and response failure criteria. Values are numbers of children.	248
APPENDIX 17 – Sensitivity analyses (primary analysis): the number children with a RTI-associated antibiotic prescription in the preceding 12 months excluding antibiotic prescriptions (a) within 14 days and (b) 56 days of the index prescription	249
APPENDIX 18 – Sensitivity analyses (primary analysis): the number children with a RTI-associated antibiotic prescription in the preceding 12 months excluding antibiotic courses for (a) children under one years old and (b) where the first criterion of our study outcome was used i.e. subsequent prescription within 14 days of the index antibiotic course)	249
APPENDIX 19 – Recruited GP practices in Oxfordshire Clinical Commissioning Group (CCG)	250
APPENDIX 20 – Promotional study material for PAUSE Study (front and reverse)	251
APPENDIX 21 – Participant information leaflet for PAUSE Study	253
APPENDIX 22 – Parent/Carer Interview Guide for PAUSE Study	256
APPENDIX 23 – Consent Form for PAUSE Study	263
APPENDIX 24 – Coding framework with candidate themes and subthemes	264
APPENDIX 25 – Coding manual with examples of typical quotes by theme, subtheme and description.....	273
APPENDIX 26 – Publication from thesis.....	285

Abstract

Antibiotic prescribing and resistance in primary care: implications for intervention

Thesis submitted for the degree of Doctor of Philosophy

Oliver van Hecke

St Hugh's College, University of Oxford

Michaelmas Term 2017

Background

Antibiotic resistance is an important societal health issue. The greatest risk factor for developing a resistant infection is antibiotic use. Almost 75% of all antibiotics in the UK are prescribed in the community, and mostly for acute respiratory tract infections (RTIs). Yet, the majority of RTIs are self-limiting, viral and do not need antibiotic treatment, especially in young children. While the effects of antibiotic-resistant infections have been widely studied in hospitals (e.g. the MRSA 'superbug'), we know less about how antibiotic-resistant infections affect people in the community, even though this is where most antibiotics are prescribed. There is also widespread public misconception about antibiotic use and resistance despite several high-profile, multimillion antibiotic awareness campaigns. This is important to address because consultation behaviour and expectations for antibiotics are a significant determinant of antibiotic use in the community.

Methods

Three studies were conducted for this thesis. First, a systematic review and meta-analysis to assess the evidence of the impact of antibiotic resistance for patients with common infections in the community; second, a retrospective analysis of routinely collected primary care data to examine the relationship between antibiotic exposure and antibiotic "response failure" in preschool children

presenting with acute RTIs; third, a qualitative interview study to explore parents' perceptions and understanding of antibiotic use and resistance when they consider consulting in the community with their preschool child who has a respiratory tract infection.

Results

Antibiotic resistance significantly impacts on patients' illness burden for common infections in the community. Patients who presented in community health care settings with antibiotic-resistant *E. coli* urinary tract infections and *S. pneumoniae* respiratory tract infections were more likely to experience delays in recovery after antibiotic treatment.

From routinely collected primary data (2009-2016), preschool children receiving two or more antibiotic courses in the previous year for acute RTIs had greater likelihood of antibiotic "response failure" to treatment for subsequent acute RTIs compared to children that had received no previous antibiotics.

When interviewing parents of young children, most parents were quite reticent about antibiotics for their children. However, very few considered antibiotic resistance as a possible harm of antibiotics. Parents thought their families were at low risk of antibiotic resistance because their families were "low users" of antibiotics and did not perceive any association between their individual consumption of antibiotics and the development and spread of antibiotic-resistant bacteria in the community. They wanted future antibiotic awareness campaigns to have a universal message relevant to their families that fit into their daily lives.

Conclusions

The findings challenge the perception that antibiotic prescribing and resistance in the community poses little or no additional risk to patients in the community, or is remote from everyday prescribing decisions. Rapid diagnostic tests and other prognostic tools need to be promoted and evaluated to better identify patients who might need an antibiotic, and reduce the risk antibiotic response failures. Clinicians and parents should exercise caution about whether further antibiotics

for acute RTIs are likely to be beneficial in those children who have received two or more antibiotic prescriptions for acute RTIs during the previous 12 months. Incorporating this into clinical practice guidelines and decision-support systems will help clinicians and parents consider a non-antibiotic strategy for acute RTIs. Future guidelines, campaigns and interventions around antibiotic resistance should tailor initiatives to outcomes that patients and clinicians in the community can relate to and slot into their daily lives. More research is needed to evaluate the impact of other common infections in primary care, and determine the relative contribution of antibiotic resistance to patients not responding to antibiotic treatment for common infections.

Acknowledgements

I would like to thank my DPhil supervisors, Professor Chris Butler, Dr Kay Wang and Dr Sarah Tonkin-Crine for their immeasurable support, patience and guidance. This thesis would only be possible through their constant inspiration and advice.

I would also like to thank the following people for contributing to the work presented in this thesis:

Nia Roberts for helping me develop the search strategies for the literature review (Chapter 2) and systematic review and meta-analysis (Chapter 4), and performing the initial database searches.

Dr Joseph Lee for helping me with the systematic review and meta-analysis (Chapter 4) by independently extracting data and assessing study quality.

Associate Professor Clare Bankhead for her tireless support in helping me develop the study protocol for the CPRD database study (Chapter 5). Mrs Alice Fuller for her wealth of database experience and patience, and performing the CPRD data cut and the bulk of the data management. Professor Richard Stevens for his abundant statistical knowledge and helping me with my sample size calculation.

Constantinos Koshari and Sarah Stevens, two fellow DPhil candidates and statisticians, who were always approachable for statistical advice and ironing out my coding problems.

Healthcare professionals and GP practices that offered to help me recruit participants for the PAUSE Study (Chapter 6). In particular, I would like to express my gratitude to Dr Christine A'Court who championed my research across the Oxfordshire Clinical Commissioning Group.

All the baby toddler groups around Oxfordshire and the many parents that gave me the opportunity to talk about the PAUSE Study, and in particular, all those parents that gave up their time to share their personal experiences.

My fellow DPhil candidates in the Gibson building for all the lunchtime “debriefing” sessions, and supporting me through my DPhil. I wish to thank my office colleagues, in particular, Dr Jenny Hirst, Merryn Voysey, Sarah Payne-Riches, Ali Albasri, Dr Ben Fletcher, Charlotte Albury and most recently Tonny Muthee for their support, banter and stimulation.

Finally, I would like to thank my parents, and my partner Jade for their unconditional love, support and encouragement.

Chapter 1 Introduction

The overall aim of this thesis is to derive better evidence of the consequences and behaviours associated with antibiotic prescribing and resistance in primary care that people in the community can relate to. Striking a chord with people in the community about “superbugs” is important to bring home the impact of antibiotic resistance.

My interest in infections and antibiotic resistance stem from my early clinical experience in a subtropical region in South Africa near the Swaziland border. I was a junior doctor working with 14 other doctors running a 200-bed district hospital. This was a time before anti-retroviral medication, where around 1 in 4 patients had HIV/AIDS and/or tuberculosis and a host of opportunistic infections. The few antibiotics we had were useless. There was not much we could do apart from relieve their suffering. Looking back many years later, I think I caught a glimpse of a post-antibiotic world often mentioned in weekly media reports of the global threat of antibiotic resistance. However, unlike HIV/AIDS, where researchers backed by huge donors, successfully tackled one virus, the threat posed by antibiotic resistance will have a significantly larger impact on human health.

I now practise in a very trendy suburb of Oxford where many people (including clinicians) have heard of the term “superbugs” and somewhat conveniently relate this to climate change or as something that happens to the unfortunate few. This is not unexpected because people in the community rarely attribute a “stubborn infection” requiring 2-3 antibiotic courses to an antibiotic-resistant infection. In the context of antibiotic resistance, the biggest culprit is that far too many antibiotics are being used for infections that will get better on their own. But unlike climate change, the impact of antibiotic resistance is a community problem where bacteria are spread between close-contacts within households and communities. Global travel means that these resistant bacteria, which might have originated in India or China, will land up here and vice-versa.

Yet clinicians (like me) managing common infections in the community are in no better position what to tell patients about antibiotic resistance that is either useful or has relevance to them. As a researcher this was immensely frustrating to me. I therefore set about thinking how I could use my DPhil as an opportunity to make a difference to millions of households and help clinicians at the coalface.

This thesis will therefore focus on assessing the evidence of the impact of antibiotic resistance relevant to the community, and attempt to show that unnecessary antibiotic use has impact in a way that people can relate to. To identify the evidence gaps and develop my specific hypotheses, I have conducted a literature review of the current evidence in this area (Chapter 2).

Chapter 2 Current practices of antibiotic prescribing and antibiotic awareness campaigns in primary care

2.1 Introduction

This chapter will give a synopsis about antibiotic prescribing in primary care against a backdrop of antibiotic resistance and antibiotic awareness campaigns. It will highlight the potential gaps in evidence and opportunities for further research.

2.2 Aims and objectives

To summarise the evidence related to antibiotic prescribing, antibiotic resistance and current antibiotic awareness strategies, relevant to a primary care context in high-income countries, with a particular focus on the United Kingdom.

2.3 Methods

To summarise the evidence pertaining to this background chapter and to identify the evidence gaps, a concise systematic search of electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science) was completed from inception to 7 November 2016 with a focus on official reports, review articles, and editorials. Search filters for “antibiotic resistance” and “primary care/community setting”, and keywords “antibiotic resistance” were used (Appendix 1).

2.4 Antibiotic prescribing in primary care

In 2015, three quarters of all antibiotics prescribed (74%) in the English NHS was in general practice.⁽¹⁾ This was followed by hospital inpatients (11%), hospital outpatients (7%), patients seen in dental practices (5%) and patients in other community settings (3%). This estimate of antibiotic use in general practice is based on oral and parenteral antibiotics (<0.1%) dispensed in

community pharmacies and includes repeat antibiotic prescriptions (e.g. patients with recurrent urinary tract infections, chronic bronchitis, or receiving long term prophylactic treatment) but does not include private antibiotic prescriptions, or topical antibiotics. It is presented using defined daily dose (DDD).

The DDD is the assumed average maintenance dose per day for a medicine used for its main indication in adults.(2) The DDD is the internationally recognised unit of measurement of medicine consumption, recommended by the World Health Organisation (WHO) and allows comparison of medicine use over time and between different countries (or locations). In general, the DDDs for antibiotics are based on their use in infections of moderate severity.

The most recent available data from general practice (2010-2015) shows that antibiotic consumption, expressed as an estimate in DDD, has decreased from 17.3 to 16.2 daily defined doses (DDD) per 1000 inhabitants per day (- 6.1%) between 2012 and 2015.(1) This translates to around 2.17 to 1.92 antibiotic items (-11.5%) prescribed per 1000 inhabitants per day across England and Wales for the same period.(1) This is in comparison to Scotland, where the use of systemic antibiotics (excluding for dental indications) was 2.05 antibiotic items per 1000 inhabitants per day where individual patient prescribing data were available for 2014.(3) Penicillins remain the most commonly prescribed antibiotic items in GP accounting for 49.8% of prescriptions, followed by tetracyclines (12.6%) and macrolides (12.6%).(1)

2.5 Appropriateness of antibiotics for respiratory tract infections

Overall, the group of infections that are most commonly treated with antibiotics are respiratory tract infections (RTIs), principally consisting of acute cough, rhinosinusitis, otitis media, sore throat and undifferentiated infections.(4-6) However, the vast majority of RTIs are spontaneously remitting illnesses often caused by viruses and antibiotics are not usually clinically indicated. There is rigorous randomised controlled trial evidence, systematically reviewed and meta-analysed from a series of Cochrane reviews, that antibiotics for these acute and generally self-

limiting infections on average reduce the duration of illness symptoms by less than one day.(7-10) For example, one third fewer children with acute otitis media had pain at day 2 to 3 (10), and the duration of sore throat and acute bronchitis (cough) was reduced by 12 to 16 hours by antibiotic treatment (numbers needed to treat to prevent one sore throat = 21).(8, 9) Yet, parents grossly overestimate the mean benefit of antibiotics on illness symptom duration for acute RTIs in children by 5 to 10 times.(11)

However, a reduction in the number of antibiotic prescriptions does not necessarily reflect more appropriate antibiotic prescribing. Improving the appropriate use of antibiotics requires an understanding of prescribing, the diagnostic process, as well as social and cultural factors that create demand in the community. In adults with acute cough or clinical features suggestive of a lower respiratory tract infection, substantial variation in antibiotic prescribing rates across 13 European countries were not associated with clinically important differences in patient recovery.(12) Furthermore, antibiotic overuse and inappropriate antibiotic prescribing persist in children with acute RTIs despite guidelines to help steer practice.(6, 13, 14) For example, Dooling et al. found substantial overuse (approximately 23% overuse) and inappropriate antibiotic selection (broad vs. narrow spectrum penicillin) for pharyngitis in children (aged 3 to 17 years) nationally in the USA between 1997 and 2010. Macrolides and other second-line antibiotics accounted for 21% and 18% of antibiotics prescribed respectively.(13) Studies from New Zealand showed that a substantial proportion of children were prescribed an antibiotic for seasonal respiratory tract infections, the majority of which are caused by viruses.(14, 15)

In the UK, Gulliford et al. analysed routinely collected data from over 500 general practices and found that the median proportion of prescribed antibiotics for 'colds and upper respiratory tract infections' was 38% in a generally low-risk group of young and middle-aged adults.(6) This is despite evidence showing that prescribing an antibiotic for upper respiratory tract infections does not decrease the rate of subsequent return visits.(16, 17) There are, of course, important issues to bear in mind when interpreting findings from routinely collected primary care data such as the question of aetiology of infection, causality or appropriateness of the antibiotic prescription.

Children are particularly likely to be prescribed antibiotics unnecessarily for several reasons: young children attending day-care have a high incidence of infections because of the unique childcare environment (i.e. young children; crowding; frequent person-to person contact)(18); most RTIs are self-limiting and viral where antibiotics are not clinically indicated (5); and children frequently consult in primary care for RTIs (19, 20), in part because parents find it difficult to judge when to seek care.(21, 22) Studies from the USA (23), and European studies (including the UK) have observed that children under 5 years old have the highest antibiotic prescribing rate.(24, 25) Moreover, antibiotic exposure is near universal by the age of 5 years in developed countries.(14) However, there is variation between GP practices in antibiotic prescribing for RTIs in primary care that is not explained by age, sex, clinical presentation, deprivation or clinician burnout or empathy (12, 26-28) that needs further evaluation.

Unnecessary antibiotic use in the community, apart from the economic cost, is a major driver for the development of antibiotic resistance (29, 30), and recent antibiotic use increases an individual's risk of developing antibiotic-resistant infections.(31, 32) Based on evidence from hospitalised patients with antibiotic-resistant infections, the consequences of resistant infections are associated with poorer clinical prognosis and greater burden on healthcare resources than antibiotic-sensitive infections: increased mortality, longer hospital stays, and increase healthcare costs.(33, 34) Here, there have been concerted antibiotic stewardship initiatives (35) as part of the UK's 5-Year Antimicrobial Resistance Strategy.(36) Under the banner of antimicrobial stewardship, primary care has become the focus of stewardship efforts in the UK (37) for the reasons outlined above.(38) However, public campaigns and interventions promoting more appropriate use of antibiotics (and antimicrobial resistance) have had limited success.(39)

2.6 Antibiotic awareness campaigns

Since the first European Awareness Day on November 18, 2008, many European countries have launched new national campaigns through their relevant health authorities.(40) Respiratory tract infections have been the target of most public campaigns since these infections account for most

of the inappropriate antibiotic prescriptions. These public campaigns have generally focussed on symptoms and directed at the public in contrast to campaigns aimed at prescribers where specific diagnoses were targeted e.g. otitis media, sinusitis. Generally, campaigns have used a top-down approach (i.e. messages delivered by health authorities) instead of a grass-roots approach (i.e. designing messages with the target audience that could be relevant, acceptable, appealing, and easy to understand and remember).(41)

Campaigns have mostly been multi-faceted (e.g. patient informational material, mass media), seasonal, and limited to a few weeks during the influenza season, targeting specific age-groups (e.g. parents of young children) and ‘at risk’ groups.(39) The most common intervention targeting the lay public was the mass distribution of patient informational material via clinicians and pharmacists for display in waiting rooms or pharmacies. The key messages in these campaigns aimed to inform the public that most respiratory tract infections are caused by viruses and thus cannot be treated by antibiotics.

Campaigns to improve the use of antibiotics primarily have targeted the knowledge, attitudes and behaviours of patients seeking, or self-medicating with antibiotics. These effects are difficult to compare because of different included populations, timeframes and definitions of exposure. Whereas the television spots in the 2001 Belgian campaign had the highest recall (79%) (42), other campaigns did not show any effect from attempts to inform the public about the differences between viral and bacterial infections.(43, 44) In the UK, there was a progressive improvement in the percentage of respondents providing a scientifically acceptable answer to the question about activity of antibiotics against coughs and colds. The percentage understanding that antibiotics do not work on most coughs and colds was 60% in 2008, 63% in 2009 and 69% in 2011. However, this improvement was accompanied by an increased expectation that their GP or nurse would prescribe them an antibiotic if they had flu (from 24% in 2008, to 26% in 2009, to 32% in 2011).(45)

A recent WHO evaluation of public-facing antibiotic awareness campaigns highlighted that the majority of campaigns were not based on behaviour-change theory and evaluations had not determined whether these interventions had the desired effect of changing the public's attitudes towards antibiotics and the impact on antibiotic resistance.(46) Campaign messages have not always been evidence-based, and have often not been sensitive to the context of each country. For example, campaign messages have often included the slogan about completing the antibiotic treatment course to prevent the development of antibiotic resistance. However, this advice has recently been called into question (47), and does not directly align itself with the fight against antibiotic resistance as the objective of finishing the treatment beyond the resolution of symptoms is prevention of relapse rather than to prevent resistance. Therefore, the cost-effectiveness of such large scale, multimillion pound campaigns to reduce antibiotic use and resistance requires further evaluation.(39)

In high-income countries such as the UK, it remains unclear whether, and which public campaign interventions result in sustained changes in public perception and behaviour about appropriate antibiotic use. Several methods have been employed for promoting more prudent use of antibiotics among prescribers, the public, or both, but the most effective approach is unknown.(48, 49) Similarly, their interaction with pre-existing public health initiatives (e.g. concurrent sepsis campaign) or confounding factors (e.g. seasonal variation in the activity of respiratory viruses) and potential adverse outcomes of reduced prescribing behaviour and public knowledge has not been well explored.

Very few public campaigns have systematically evaluated their effect on bacterial resistance to antibiotics. A recent WHO survey in 2016 found that 36/60 antibiotic awareness campaigns from high-income and low and middle-income countries had no evaluation process.(46) Campaigns in Belgium and France were associated with a decrease in antibiotic use by 36% over the winter season 2006-7, and 26.5% over 2003-7 respectively (50, 51), with a substantial reduction in penicillin, tetracycline and macrolide resistance in *Streptococcus pneumoniae*. Evaluation of

campaigns like this is important because it is one of the few ways to assess whether efforts to reduce unnecessary antibiotic prescribing and antibiotic resistance are working.

Yet, intuitively, the outcome of public campaigns - promoting the appropriate use of antibiotics - seems easy to measure: a reduction in the number of antibiotic prescriptions that consequently slows the development and spread of antibiotic-resistant bacteria. However, this view may be over simplistic. There are a number of stepping stones: campaigns messages are firstly received by the intended audience; the message enhances the quality of prescribing and outcome expectations; the message then enables the respective audience to change their behaviour by using fewer antibiotics, or better antibiotic choice for an optimum duration; with no negative effect on patient outcomes; and lastly reducing antibiotic resistance – which depends on the microorganisms and antibiotics tested.

Therefore the outcome of public campaigns is less straightforward (16), and may be one of the reasons why it is difficult to assess the impact of antibiotic resistance on clinical outcomes against a background of unnecessary antibiotic use using routinely collected observational data over short periods of time.(52)

2.7 Public misconceptions about antibiotic resistance

Public understanding of antibiotics and resistance is important because consultation behaviour and expectations for antibiotics are a significant determinant of inappropriate antibiotic use.(53)

In the UK, as in many countries, access to almost all antibiotics requires a prescription from a medical practitioner. However, there is also a small contingent of patients who bypass the clinician's gatekeeper role by self-medicating: either using previously issued prescriptions or sharing antibiotics with friends and family.(54) There is also growing body of evidence that certain antibiotics are purchased online without a prescription in the UK (amoxicillin, doxycycline, metronidazole) often failing to reach quality standards.(Mutinga T 2017 DPhil thesis)(55)

Although previous public campaigns in the UK, such as CATNAP (Campaign on Antibiotic Treatment and National Advice to the Public) and ‘Andybiotic’ have improved patients’ knowledge about the need to avoid unnecessary antibiotic use (54, 56, 57), misconceptions about antibiotic resistance persist. Individuals with better knowledge of when antibiotic should be used still report being able to obtain antibiotic without prescription and self-treat with antibiotics.(54)

Research suggests that the general public do not perceive a link between resistant bacteria (e.g. “superbugs”) and antibiotic use.(58-62). This is reflected in disappointing results of national and international antimicrobial campaigns.(39, 54) Although awareness of the term “antibiotic resistance” may be relatively high, there are multiple interpretations of the term, often misconceived as a change in the human body rather than in bacteria.(53, 58, 60) Importantly, patients believe they are at low personal risk of antibiotic resistance and that their risk is only increased if they are hospitalised, or use antibiotics long-term.(59) Often the blame is attributed to ‘other’, ‘irresponsible’ patients who misuse or overuse antibiotics, or to overprescribing by GPs.(59) These ‘irresponsible’ patients have been characterized as needlessly using antibiotics, failing to complete the antibiotic course, disposing of unwanted antibiotics inappropriately or giving unused antibiotics to others. People are also likely to disengage from information about antibiotic resistance as they view it as a phenomenon outside of their personal control and/or the responsibility of government or society in general.(59, 60)

As outlined above, previous campaigns have often followed a top-down approach, with messages delivered to the public by experts with little regard for the context in which people live.(39) So, for example, campaigns that simply tell the public not to use antibiotics inappropriately do not take into account a parent investing time in taking their ill child to the GP and who cannot afford to take more time off work to come back again to see the doctor if a non-antibiotic treatment strategy doesn’t work.(63, 64) This approach can limit engagement with campaign messages at an individual level and subsequently have little impact on knowledge, understanding or any resulting behaviour change.(46)

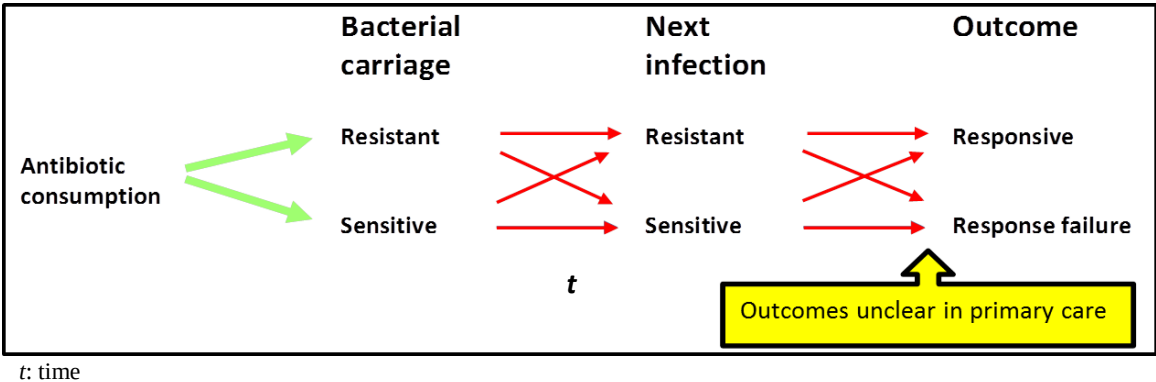
2.8 Current evidence for antibiotic resistance in primary care

2.8.1 Antibiotic resistance

Antibiotic resistance is the ability of bacteria to resist the effects of an antibiotic.(65) Antibiotic resistance occurs when bacteria change in ways that reduces or eliminates the effectiveness of antibiotics designed to cure or prevent infections. The bacteria survive and continue to multiply causing more harm. This leads to antibiotics becoming less effective over time and in many extreme cases, ultimately useless.

Antibiotic resistance is a complex issue that depends on the type of bacterial microorganism, specific patient, and antibiotic used.(66) Put simply, “antibiotic resistance” is measured in-vitro in a laboratory and based on guidelines reached through consensus, whilst the effects of resistant bacteria occurs in-vivo and seen in hospitals and the community. This distinction is important because a laboratory-focused, microbiological definition of antibiotic resistance is often incorrectly equated to the clinical effects seen in patients with resistant bacterial infections. Thus, our understanding is less clear about how patients actually respond to resistant bacteria when they become ill with common infections in the community.

Figure 1 Pathway from antibiotic consumption to clinical outcome



2.8.2 Why antibiotic resistance occurs

The emergence of antibiotic resistance in bacteria is a natural Darwinian selection process or response. Antibiotics kill sensitive bacteria and thus allow resistant bacteria to fill that niche. Yet, this evolutionary bacterial response is amplified by antibiotic exposure in health care, agriculture and the environment. Antibiotics likely affect not only the sensitivity but the timing (*t*) of the next infection (Fig 1). The onward transmission of resistant bacteria and a decline in infectious disease mortality is mainly the result of improvements in a number of social determinants of health.(67) Examples include standards of infection control, sanitation, access to clean water, access the quality-assured antimicrobials and diagnostics, travel, and migration.(68)

In clinical medicine, the human microbiome has been exposed to unprecedented high concentrations of antibiotic use. Although the concentration of antibiotic prescribing might be highest in inpatient settings, with 30-40% of patients on antibiotics in European hospitals (69), it is the community where the greatest quantity of antimicrobial prescribing occurs.(70)

2.8.3 The link between antibiotic use and antibiotic resistance in the community

Although there are other drivers for antibiotic resistance e.g. antibiotic use in agriculture and livestock ingested by humans when they consume food (71), or potentially non-antibiotic antimicrobials (triclosan) in antibacterial soaps (72), antibiotic use in human medicine is the most important risk factor for carriage of antibiotic-resistant bacteria.(29, 73) For example, in a meta-analysis of respiratory tract infections in adults and children (7 studies; 2,605 participants), the pooled odds ratios for resistance were 2·4 [95% confidence interval (CI) 1·4 to 3·9] within 2 months of antibiotic treatment and 2·4 (1·3 to 4·5] within 12 months.(29)

Although the link between antibiotic use and resistant bacterial carriage may seem straightforward, this association is far more complex.(30, 31) In a study of 19 European countries, although the correlation between community use of penicillin and penicillin resistance was 0.84, the ‘dose-response’ association was not clear cut.(30) For example, in France, the rate of

penicillin prescribing is 2.5 times that in the United Kingdom but the proportion of non-susceptible *Streptococcus pneumoniae* was found to be 10 times higher (40% v 4%).(30)

Therefore, antibiotic resistance will depend on the pattern of antibiotic use in a country, various pharmacodynamic variables such as the specific interaction between bacterium and drug, the interaction between bacterium and host, bacterial mutation rates, the potential for transmission, cross-resistance, selection of co-resistance to unrelated antibiotics, and the stage the country or geographic region is at in the evolution of resistance.(31, 68) For example, Sweden and Denmark have higher rates of penicillin prescribing than the UK but lower resistance, while Finland has lower prescribing but higher resistance.(30) However, resistance data in the UK is not based on routinely collected samples. Resistance data is based on surveillance systems of pathogens from patients with septicaemia in hospitals with particular focus on *Escherichia coli*, other Gram-negative bacteria and staphylococcal bacteraemia.(1) Therefore, we have an ecological fallacy where we infer that resistance will affect individual patients in the community based on aggregate group data from patients in hospitals who may or may not have taken antibiotics.

The role of antibiotic use in driving the emergence of resistance is likely to be specific to each drug and to each organism, the ease with which resistance elements are transferred between bacteria and between species, and the effect of changes in antibiotic use.(68) Yet this is only one side of coin. At a human population level, there are important public health factors such as rates of vaccine uptake, different health care systems and social norms (e.g. the number of children in day-care centres), human migration and tourism, sanitation, and population densities that influence the prevalence of resistance.(74)

In 2017, the WHO published its first ever list of antibiotic-resistant "priority pathogens" (Fig. 2) – a catalogue of 12 families of bacteria that pose the greatest threat to human health globally.(75) Whereas the threat of some bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA) has come down in the UK (1), the WHO list highlights the threat of gram-negative bacteria that are resistant to multiple antibiotics and that resistance is increasing. With this list in mind, the scope

of future campaigns should be expanded to cover bacteria causing urinary tract infections and sexually transmitted diseases.(75)

Figure 2 WHO global priority list of antibiotic-resistant bacteria

Priority 1: CRITICAL	<i>Acinetobacter baumannii</i> <i>Pseudomonas aeruginosa</i> <i>Enterobacteriaceae</i> *
Priority 2: HIGH	<i>Enterococcus faecium</i> <i>Staphylococcus aureus</i> <i>Helicobacter pylori</i> <i>Campylobacter</i> <i>Salmonella</i> <i>Neisseria gonorrhoeae</i>
Priority 3: MEDIUM	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenza</i> <i>Shigella</i>

* *Enterobacteriaceae* include: *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp. *Proteus* spp., and *Providencia* spp, *Morganella* spp.

2.8.4 How quickly does antibiotic resistance develop?

The impact of antibiotic prescribing on resistance in individuals in the community suggests that the effect occurs rapidly but that it is transient. For example, a prospective controlled study in the UK in children with an acute respiratory tract infection observed that prescribing amoxicillin to a child in general practice doubled the risk of recovering a β lactamase encoding resistance element two weeks later, but recovered to the level seen before treatment within 12 weeks.(31) This is supported by a twofold increase in the odds of recovery of penicillin-resistant pneumococci from children who had received a β lactam antibiotic within two months but not six months from a study with Australian children.(76) Older studies, also in children, confirm that β lactam-producing bacteria were present one week after antibiotic treatment of otitis media or pharyngitis (77), and another study from Malawi in 2000, reported recovery of cotrimoxazole-resistant pneumococci one week after malaria treatment with cotrimoxazole.(78)

These study findings are supported by a systematic review by Costelloe et al. where the effect of prescribed antibiotics for respiratory or urinary infections in primary care (in both adults and

children) is greatest in the month immediately after treatment but may persist for up to 12 months.(29) The authors point out that, in contrast to urinary tract infections where there was a clear time trend, there was no association between resistance and time for respiratory tract infections (β coefficient of -0.01 [95% CI -0.26 to 0.24 , $P=0.91$; 7 studies]). However, another larger systematic review of 243 studies suggests that the relationship between antibiotic consumption and resistance is also variable within a study depending on which bacteria were being considered.(73) Therefore, a study looking at multiple types of bacteria may have found a positive relationship between antibiotic consumption and resistance for one bacterium, but a negative relationship for another. This emphasises that antibiotic resistance is a property of bacteria, specific to each bacteria where one size does not fit all.

It further highlights that observational studies are not necessarily useful because they are plagued by population-based confounders where even antibiotics of the same class vary widely in effects on the selection of resistant organisms.(32) Therefore, randomised controlled trials are needed to address this issue of which there are very few.(32, 79) For example, in the randomised controlled trial by Malhotra-Kumar et al., the majority of the streptococci exhibiting resistance to amoxicillin were rather short-lived lasting around 4 weeks post-therapy compared with the placebo group.(79)

2.8.5 The reversibility of antibiotic resistance

The reversibility of antibiotic resistance after withdrawal or reduction of antibiotic use in humans has proven difficult in practice and the effects are not that clear-cut in the community.(80) On the one hand, there is evidence that supports the correlation between reduced antibiotic use and a decrease in antibiotic resistance. For example, in a French prospective trial involving children aged 3-5 years old attending day-care, a reduction in antibiotic use over a 5-month period significantly decreased pharyngeal carriage of penicillin-non-susceptible *S. pneumoniae* (PNSP).(81) In Iceland, the reductions and changes in antibiotic consumption together with restrictions on day-care centre attendance for children colonized with non-susceptible *S.*

pneumoniae resulted in a transient decrease in the frequency of PNSP.(82) However, continued conservative use of antibiotics was not accompanied by a sustained low level of PNSP. In a UK primary care setting, the reduction in antibiotic use has resulted in decreased resistance frequencies in *Escherichia coli*. Butler et al. showed that the general practices with the greatest reduction in ampicillin and trimethoprim prescriptions during a 7-year follow-up period, also experienced a decrease in the corresponding resistance in *Escherichia coli* in urine samples submitted from their practice populations.(83)

By contrast, there is also evidence where reduced antibiotic use has not translated to a decrease in antibiotic resistance. A voluntary restriction on trimethoprim-containing antibiotics (85% reduction) in one county in Sweden over a 24-month period starting in 2004 resulted in only a marginal slowing of the rise in trimethoprim resistance in uropathogenic *Escherichia coli*.(84) In another Swedish study, during a 10-year study period (1994–2004), the overall prescribing of antibiotics decreased by 28%, yet this was not associated with a decrease in the incidence of PNSP.(85) Similarly, a national restriction (98% reduction) of cotrimoxazole prescribing in the UK, was not associated with a reduction in the prevalence of sulphonamide resistance in *Escherichia coli* but rather a 6% increase in sulphonamide resistance.(86)

There are several explanations why there is no clear correlation between reduced antibiotic use and decreased antibiotic resistance. One factor at a population level is the dynamic influx and outflow of populations living in a connected global world. Another factor, at the level of bacteria, is the potential for resistance elements to be transmitted through bacterial populations both "vertically," when new generations inherit antibiotic resistance genes, and "horizontally," when bacteria share or exchange sections of genetic material between similar bacteria and between different bacterial species.(68, 87) Horizontal gene transfer is the primary mechanism of acquiring antibiotic resistance. Therefore, although there is evidence to show that reducing antibiotic use reduces resistance at the individual level, we are less certain that this correlation is applicable at a population level.

This suggests that bacteria can readily acquire resistance determinants, and that cross selection and co-selection of these resistance determinants are highly pertinent, and might persist at low but detectable levels for many years. This means that we should not expect dramatic changes in resistance rates in the community even after major antibiotic interventions. However, these interventions will delay the development of antibiotic resistance.

2.8.6 The evidence gaps

On a population level, there are a number of gaps in our understanding of antibiotic resistance. For example, it is unclear how the flow of movement of patients and our built environment affects human-human transmission, within and between healthcare institutions (68), and even community reservoirs like day-care and care home settings. The absence of basic knowledge about ideal prescribing regimens and our understanding of how to optimise antibiotic use represent a significant gap.(88) This approach will likely entail detailed analysis for specific groups of patients (e.g. infants, pregnant women, obese and co-infected patients) relevant to specific bacteria and infection types.

Addressing public misconceptions about antibiotic resistance and the role of antibiotics for common infections is important to break the cycle of inappropriate antibiotic use. This will mean displaying better information quickly, clearly and reliably for patients, quantifying the risks versus benefits of using antibiotics for self-limiting illnesses. Additionally, educating patients about self-management strategies and potential indicators of serious illness may give them more confidence in looking after themselves and their loved ones.

To optimise antibiotic use and reduce diagnostic uncertainty, improved rapid diagnostic tests are needed to identify the aetiology of pathogenic organism, the potential benefit from antibiotics, and resistant bacteria. For primary care in particular, early evidence suggests that rapid diagnostic tests used in a community-setting can guide antibiotic prescribing for community-acquired

respiratory tract infections (89-91), and more research is needed for urinary tract infections.(92, 93)

There also needs to be a greater level of detail from community infection surveillance to identify associations between antibiotic use and misuse, and to identify successful interventions.(94)

Often these surveillance data are rarely standardised or reported in a timely manner, or are aggregated, which makes interpretation at the level of the individual patient of little use. To develop an effective strategy to manage antibiotic resistance in the community we need to understand what is happening at the level of the individual patient and close-contact transmission between individuals (e.g. family), not just to inform patient care but also to provide firm estimates for the population models that should inform policy on antibiotic prescribing.(31)

2.8.7 Better evidence to ensure long-term effectiveness of antibiotics

Although the above mentioned gaps are important, engaging policy makers, antibiotic prescribers, patients and the public are as important to ensure sustainable access and effectiveness of antibiotics. Improving the quality of antibiotic prescribing and reducing consumption are the most important actions needed to slow the development and spread of antibiotic-resistant bacteria.

However, as summarised above, public campaigns and interventions promoting more appropriate use of antibiotics have had limited success, and have not had the desired effect of stemming the tide of inappropriate prescribing and antibiotic resistance. Theoretical predictions about the potential consequences of antibiotic resistance for future generations can seem abstract (95), and remote to individuals with common infections facing treatment decisions in the here and now.(62) It is therefore not surprising that members of the public do not relate their antibiotic consumption to antibiotic resistance and a risk to their own health and their communities.(58, 62) Likewise, primary care clinicians report that they rarely encounter treatment failure because of antibiotic resistance, leading to the perception that antibiotic resistance is remote from prescribing decisions. (96, 97)

This major evidence gap may influence expectations for antibiotics and antibiotic prescribing decisions in the community.(98, 99) Therefore, the clinical relevance of antibiotic resistance for common infections is of far greater relevance to patients and clinicians in the community and remains unknown. This is a critical aspect that public campaigns have not been able to incorporate into their message. Chapter 4 will discuss these implications of antibiotic resistance for common infections in the community in terms of practical and clinically-relevant outcomes for patients and clinicians, and move beyond a laboratory-focused, microbiological outcome.

Chapter 3 gives a brief overview of the overall structure and specific objectives of this thesis.

2.9 References

1. Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) 2010-2015. London; 2016.
2. World Health Organisation (WHO). DDD: Definition and general considerations 2016 [updated 20/12/2016. Available from: https://www.whooc.no/ddd/definition_and_general_considera/.
3. Health Protection Scotland and Information Services Division. Report on Antimicrobial Use and Resistance in Humans in 2014.: Health Protection Scotland and Information Services Division; 2015.
4. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. *The Journal of antimicrobial chemotherapy*. 2014;69(1):234-40.
5. National Institute for Health and Clinical Excellence. Respiratory Tract Infections - Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care. London: National Institute for Health and Clinical Excellence (UK); 2008.
6. Gulliford MC, Dregan A, Moore MV, Ashworth M, Staa T, McCann G, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. *BMJ open*. 2014;4(10):e006245.
7. Arroll B, Kenealy T. Antibiotics for the common cold. *The Cochrane database of systematic reviews*. 2002(3):Cd000247.
8. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *The Cochrane database of systematic reviews*. 2014(3):Cd000245.
9. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *The Cochrane database of systematic reviews*. 2013(11):Cd000023.
10. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *The Cochrane database of systematic reviews*. 2015(6):Cd000219.
11. Coxeter PD, Mar CD, Hoffmann TC. Parents' Expectations and Experiences of Antibiotics for Acute Respiratory Infections in Primary Care. *Annals of family medicine*. 2017;15(2):149-54.
12. Butler CC, Hood K, Verheij T, Little P, Melbye H, Nuttall J, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ (Clinical research ed)*. 2009;338:b2242.

13. Dooling KL, Shapiro DJ, Van Beneden C, Hersh AL, Hicks LA. Overprescribing and inappropriate antibiotic selection for children with pharyngitis in the United States, 1997-2010. *JAMA Pediatrics*. 2014.
14. Hobbs MR, Grant CC, Ritchie SR, Chelimo C, Morton SMB, Berry S, et al. Antibiotic consumption by New Zealand children: exposure is near universal by the age of 5 years. *The Journal of antimicrobial chemotherapy*. 2017;72(6):1832-40.
15. Williamson DA, Roos R, Verrall A, Smith A, Thomas MG. Trends, demographics and disparities in outpatient antibiotic consumption in New Zealand: a national study. *The Journal of antimicrobial chemotherapy*. 2016;71(12):3593-8.
16. Hurlimann D, Limacher A, Schabel M, Zanetti G, Berger C, Muhlemann K, et al. Improvement of antibiotic prescription in outpatient care: a cluster-randomized intervention study using a sentinel surveillance network of physicians. *The Journal of antimicrobial chemotherapy*. 2014.
17. Li J, De A, Ketchum K, Fagnan LJ, Haxby DG, Thomas A. Antimicrobial prescribing for upper respiratory infections and its effect on return visits. *Family medicine*. 2009;41(3):182-7.
18. Rooshenas L, Wood F, Brookes-Howell L, Evans MR, Butler CC. The influence of children's day care on antibiotic seeking: a mixed methods study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2014;64(622):e302-12.
19. Hippisley-Cox J, Vinogradova Y. Q research. Trends in consultation rates in general practice 1995/1996 to 2008/2009: Analysis of the QResearch1 database. Final Report to the NHS Information Centre and Department of Health, Nottingham. NHS The Information Centre for Health and Social Care, University of Nottingham; 2009.
20. Sands R, Shanmugavadivel D, Stephenson T, Wood D. Medical problems presenting to paediatric emergency departments: 10 years on. *Emergency medicine journal : EMJ*. 2012;29(5):379-82.
21. Kai J. What worries parents when their preschool children are acutely ill, and why: a qualitative study. *BMJ (Clinical research ed)*. 1996;313(7063):983-6.
22. Neill SJ, Jones CH, Lakhanpaul M, Roland DT, Thompson MJ. Parents' help-seeking behaviours during acute childhood illness at home: A contribution to explanatory theory. *Journal of child health care : for professionals working with children in the hospital and community*. 2016;20(1):77-86.
23. Kronman MP, Zhou C, Mangione-Smith R. Bacterial prevalence and antimicrobial prescribing trends for acute respiratory tract infections. *Pediatrics*. 2014;134(4):e956-65.
24. de Bont EG, van Loo IH, Dukers-Muijers NH, Hoebe CJ, Bruggeman CA, Dinant GJ, et al. Oral and topical antibiotic prescriptions for children in general practice. *Archives of disease in childhood*. 2013;98(3):228-31.
25. Majeed A, Moser K. Age- and sex-specific antibiotic prescribing patterns in general practice in England and Wales in 1996. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 1999;49(446):735-6.
26. Hawker JJ, 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. *The Journal of antimicrobial chemotherapy*. 2014;69(12):3423-30.
27. Ashworth M, Charlton J, Ballard K, Latinovic R, Gulliford M. 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(517):603-8.
28. Sun BZ, Chaitoff A, Hu B, Neuendorf K, Manne M, Rothberg MB. Empathy, burnout, and antibiotic prescribing for acute respiratory infections: a cross-sectional primary care study in the US. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2017;67(661):e565-e71.
29. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2010;340:c2096.

30. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* (London, England). 2005;365(9459):579-87.
31. Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R, et al. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ* (Clinical research ed). 2007;335(7617):429.
32. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* (London, England). 2007;369(9560):482-90.
33. de Kraker ME, Davey PG, Grundmann H. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS medicine*. 2011;8(10):e1001104.
34. de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. *The Journal of antimicrobial chemotherapy*. 2011;66(2):398-407.
35. Johnson AP, Ashiru-Oredope D, Beech E. Antibiotic Stewardship Initiatives as Part of the UK 5-Year Antimicrobial Resistance Strategy. *Antibiotics* (Basel, Switzerland). 2015;4(4):467-79.
36. Department of Health. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. 2013.
37. Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance. *The Path of Least Resistance*. London; 1998.
38. Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. *Lancet* (London, England). 2016;387(10029):1743-52.
39. Huttner B, Goossens H, Verheij T, Harbarth S. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *The Lancet Infectious diseases*. 2010;10(1):17-31.
40. Earnshaw S, Monnet DL, Duncan B, O'Toole J, Ekdahl K, Goossens H. European Antibiotic Awareness Day, 2008 - the first Europe-wide public information campaign on prudent antibiotic use: methods and survey of activities in participating countries. *Euro Surveill*. 2009;14(30):19280.
41. Formoso G, Paltrinieri B, Marata AM, Gagliotti C, Pan A, Moro ML, et al. Feasibility and effectiveness of a low cost campaign on antibiotic prescribing in Italy: community level, controlled, non-randomised trial. *BMJ : British Medical Journal*. 2013;347.
42. Goossens H, Guillemot D, Ferech M, Schlemmer B, Costers M, van Breda M, et al. National campaigns to improve antibiotic use. *European journal of clinical pharmacology*. 2006;62(5):373-9.
43. Curry M, Sung L, Arroll B, Goodyear-Smith F, Kerse N, Norris P. Public views and use of antibiotics for the common cold before and after an education campaign in New Zealand. *The New Zealand medical journal*. 2006;119(1233):U1957.
44. National Information Program on Antibiotics. What do Canadians think? 2002 [Available from: http://www.antibiotics-info.org/can_tnk.html].
45. McNulty C, Joshi P, Butler CC, Atkinson L, Nichols T, Hogan A, 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(2):e000674.
46. Saam M, Huttner B, Harbarth S. Evaluation of antibiotic awareness campaigns. Geneva: WHO Collaborating Centre on Patient Safety; 2017.
47. Llewelyn MJ, Fitzpatrick JM, Darwin E, Sarah-Tonkin-Crine, Gorton C, Paul J, et al. The antibiotic course has had its day. *BMJ* (Clinical research ed). 2017;358.
48. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *The Cochrane database of systematic reviews*. 2005(4):CD003539.

49. Ranji SR, Steinman MA, Shojania KG, Gonzales R. Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis. *Medical care*. 2008;46(8):847-62.
50. Goossens H, Coenen S, Costers M, De Corte S, De Sutter A, Gordts B, et al. Achievements of the Belgian Antibiotic Policy Coordination Committee (BAPCOC). *Euro Surveill*. 2008;13(46).
51. Sabuncu E, David J, Bernede-Bauduin C, Pepin S, Leroy M, Boelle PY, et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. *PLoS medicine*. 2009;6(6):e1000084.
52. Currie CJ, Berni E, Jenkins-Jones S, Poole CD, Ouwens M, Driessen S, et al. Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. *BMJ (Clinical research ed)*. 2014;349:g5493.
53. Norris P, Chamberlain K, Dew K, Gabe J, Hodgetts D, Madden H. Public Beliefs about Antibiotics, Infection and Resistance: A Qualitative Study. *Antibiotics (Basel, Switzerland)*. 2013;2(4):465-76.
54. McNulty CA, Boyle P, Nichols T, Clappison P, Davey P. Don't wear me out--the public's knowledge of and attitudes to antibiotic use. *The Journal of antimicrobial chemotherapy*. 2007;59(4):727-38.
55. Boyd SE, Moore LSP, Gilchrist M, Costelloe C, Castro-Sanchez E, Franklin BD, et al. Obtaining antibiotics online from within the UK: a cross-sectional study. *The Journal of antimicrobial chemotherapy*. 2017;72(5):1521-8.
56. Parsons S, Morrow S, Underwood M. Did local enhancement of a national campaign to reduce high antibiotic prescribing affect public attitudes and prescribing rates? *The European journal of general practice*. 2004;10(1):18-23.
57. Woodhead M, Finch R. Public education - a progress report. *The Journal of antimicrobial chemotherapy*. 2007;60 Suppl 1:i53-5.
58. Brookes-Howell L, Elwyn G, Hood K, Wood F, Cooper L, Goossens H, et al. 'The body gets used to them': patients' interpretations of antibiotic resistance and the implications for containment strategies. *Journal of general internal medicine*. 2012;27(7):766-72.
59. Brooks L, Shaw A, Sharp D, Hay AD. Towards a better understanding of patients' perspectives of antibiotic resistance and MRSA: a qualitative study. *Family practice*. 2008;25(5):341-8.
60. Hawkings NJ, Wood F, Butler CC. Public attitudes towards bacterial resistance: a qualitative study. *The Journal of antimicrobial chemotherapy*. 2007;59(6):1155-60.
61. Jin CG, Ely A, Fang LJ, Liang XY. Framing a global health risk from the bottom-up: User perceptions and practices around antibiotics in four villages in China. *Health Risk & Society*. 2011;13(5):433-49.
62. McCullough AR, Parekh S, Rathbone J, Del Mar CB, Hoffmann TC. A systematic review of the public's knowledge and beliefs about antibiotic resistance. *The Journal of antimicrobial chemotherapy*. 2016;71(1):27-33.
63. Chaintarli K, Ingle SM, Bhattacharya A, Ashiru-Oredope D, Oliver I, Gobin M. Impact of a United Kingdom-wide campaign to tackle antimicrobial resistance on self-reported knowledge and behaviour change. *BMC Public Health*. 2016;16:393.
64. Kesten JM, Bhattacharya A, Ashiru-Oredope D, Gobin M, Audrey S. The Antibiotic Guardian campaign: a qualitative evaluation of an online pledge-based system focused on making better use of antibiotics. *BMC Public Health*. 2017;18(1):5.
65. Centers for Disease Control and Prevention. Antibiotic Resistance Questions and Answers 2015 [Available from: <http://www.cdc.gov/getsmart/community/about/antibiotic-resistance-faqs.html>].
66. Diene SM, Abat C, Rolain J-M, Raoult D. How artificial is the antibiotic resistance definition? *The Lancet Infectious Diseases*. 2017;17(7):690.
67. Cosby JL, Francis N, Butler CC. The role of evidence in the decline of antibiotic use for common respiratory infections in primary care. *The Lancet Infectious diseases*. 2007;7(11):749-56.

68. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* (London, England). 2016;387(10014):176-87.
69. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals, 2011–2012. Stockholm. 2013.
70. European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm; 2014.
71. The Review on Antimicrobial Resistance. Antimicrobials in agriculture and the environment: reducing unnecessary use and waste. 2015.
72. Webber MA, Buckner MMC, Redgrave LS, Ifill G, Mitchenall LA, Webb C, et al. Quinolone-resistant gyrase mutants demonstrate decreased susceptibility to triclosan. *Journal of Antimicrobial Chemotherapy*. 2017;72(10):2755-63.
73. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis*. 2014;14:13.
74. Turnidge J, Christiansen K. Antibiotic use and resistance--proving the obvious. *Lancet* (London, England). 2005;365(9459):548-9.
75. World Health Organisation. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva; 2017 27 February 2017.
76. Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM. Effect of beta lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. *BMJ* (Clinical research ed). 2002;324(7328):28-30.
77. Brook I. Emergence and persistence of beta-lactamase-producing bacteria in the oropharynx following penicillin treatment. *Archives of otolaryngology--head & neck surgery*. 1988;114(6):667-70.
78. Feikin DR, Dowell SF, Nwanyanwu OC, Klugman KP, Kazembe PN, Barat LM, et al. Increased carriage of trimethoprim/sulfamethoxazole-resistant *Streptococcus pneumoniae* in Malawian children after treatment for malaria with sulfadoxine/pyrimethamine. *The Journal of infectious diseases*. 2000;181(4):1501-5.
79. Malhotra-Kumar S, Van Heirstraeten L, Coenen S, Lammens C, Adriaenssens N, Kowalczyk A, et al. Impact of amoxicillin therapy on resistance selection in patients with community-acquired lower respiratory tract infections: a randomized, placebo-controlled study. *The Journal of antimicrobial chemotherapy*. 2016;71(11):3258-67.
80. Sundqvist M. Reversibility of antibiotic resistance. *Uppsala journal of medical sciences*. 2014;119(2):142-8.
81. Guillemot D, Varon E, Bernède C, Weber P, Henriot L, Simon S, et al. Reduction of Antibiotic Use in the Community Reduces the Rate of Colonization with Penicillin G—Nonsusceptible *Streptococcus pneumoniae*. *Clinical Infectious Diseases*. 2005;41(7):930-8.
82. Kristinsson KG. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. *Microbial drug resistance* (Larchmont, NY). 1997;3(2):117-23.
83. Butler CC, Dunstan F, Heginbotham M, Mason B, Roberts Z, Hillier S, et al. Containing antibiotic resistance: decreased antibiotic-resistant coliform urinary tract infections with reduction in antibiotic prescribing by general practices. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2007;57(543):785-92.
84. Sundqvist M, Geli P, Andersson DI, Sjölund-Karlsson M, Runeheggen A, Cars H, et al. Little evidence for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use. *Journal of Antimicrobial Chemotherapy*. 2010;65(2):350-60.
85. Nilsson P, Laurell MH. A 10-year follow-up study of penicillin-non-susceptible *S. pneumoniae* during an intervention programme in Malmö, Sweden. *Scandinavian journal of infectious diseases*. 2006;38(10):838-44.
86. Enne VI, Livermore DM, Stephens P, Hall LMC. Persistence of sulphonamide resistance in *Escherichia coli* in the UK despite national prescribing restriction. *The Lancet*. 2001;357(9265):1325-8.

87. Martinez JL. Environmental pollution by antibiotics and by antibiotic resistance determinants. *Environmental pollution* (Barking, Essex : 1987). 2009;157(11):2893-902.
88. Llewelyn MJ, Fitzpatrick JM, Darwin E, SarahTonkin C, Gorton C, Paul J, et al. The antibiotic course has had its day. *BMJ (Clinical research ed)*. 2017;358:j3418.
89. Minnaard MC, van de Pol AC, Hopstaken RM, van Delft S, Broekhuizen BD, Verheij TJ, et al. C-reactive protein point-of-care testing and associated antibiotic prescribing. *Family practice*. 2016;33(4):408-13.
90. Cals JW, Butler CC, Hopstaken RM, Hood K, Dinant GJ. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ (Clinical research ed)*. 2009;338:b1374.
91. Tonkin-Crine SKG, Wang K, van Hecke O, Roberts NW, McCullough A, Hansen MP, et al. Clinician-targeted interventions to reduce antibiotic prescribing for acute respiratory infections in primary care: an overview of systematic reviews. *Cochrane Database of Systematic Reviews*. 2016(6).
92. Holm A, Cordoba G, Sorensen TM, Jessen LR, Siersma V, Bjerrum L. Point of care susceptibility testing in primary care - does it lead to a more appropriate prescription of antibiotics in patients with uncomplicated urinary tract infections? Protocol for a randomized controlled trial. *BMC Fam Pract*. 2015;16:106.
93. Hullegie S, Wootton M, Verheij TJ, Thomas-Jones E, Bates J, Hood K, et al. Clinicians' interpretations of point of care urine culture versus laboratory culture results: analysis from the four-country POETIC trial of diagnosis of uncomplicated urinary tract infection in primary care. *Family practice*. 2017.
94. Anderson EC, Ingle SM, Muir P, Beck C, Finn A, Leeming JP, et al. Community paediatric respiratory infection surveillance study protocol: a feasibility, prospective inception cohort study. *BMJ open*. 2016;6(8):e013017.
95. The Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: final report and recommendations. 2016.
96. Fletcher-Lartey S, Yee M, Gaarslev C, Khan R. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. *BMJ open*. 2016;6(10):e012244.
97. Simpson SA, Wood F, Butler CC. General practitioners' perceptions of antimicrobial resistance: a qualitative study. *The Journal of antimicrobial chemotherapy*. 2007;59(2):292-6.
98. Wood F, Simpson S, Butler CC. Socially responsible antibiotic choices in primary care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluoroquinolone antibiotics. *Family practice*. 2007;24(5):427-34.
99. Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2015;65(639):e702-7.

Chapter 3 Aims, objectives and structure of thesis

3.1 Aims and objectives

The overall aim of this thesis is to address the knowledge gaps identified in Chapter 2 by assessing the consequences and behaviours associated with antibiotic prescribing and resistance in the community. Identifying these evidence gaps will inform the design and implementation of interventions that aim to reduce antibiotic prescribing and resistance, and help improve shared decision-making strategies for antibiotic prescribing. To address the complexities associated with antibiotic prescribing and antibiotic use in the community, I have used a mixed methods approach.

The specific objectives are:

1. To assess the evidence base of the impact of antibiotic resistance on clinical outcomes and primary care workload in patients presenting with respiratory tract, urinary tract or skin infections in the community (Chapter 4)
2. To examine the relationship between antibiotic exposure and antibiotic “response failure” in children presenting with acute respiratory tract infections in primary care (Chapter 5)
3. To explore parents’ perceptions and understanding of antibiotic use and resistance when consulting in the community for children with respiratory tract infections (Chapter 6)

3.2 Overall structure of thesis and studies to address objectives

Chapter 4: The implications of antibiotic resistance for patients’ recovery from common infections in the community: a systematic review and meta-analysis

This chapter identifies existing research evidence concerning the impact and clinical relevance of antibiotic resistance on patient recovery and healthcare utilisation in patients presenting with respiratory tract, urinary tract or skin and soft tissue infections in the community based on published and unpublished data from observational studies and randomised controlled trials.

Chapter 5: The relationship between antibiotic exposure and antibiotic “response failure” in children presenting with acute respiratory tract infections (RTI) in primary care: an observational cohort study

By analysing routinely collected data from UK primary care, this chapter explores whether higher levels of antibiotic exposure in preschool children who present in primary care with acute respiratory tract infections is associated with an increased likelihood of subsequent respiratory tract infections that do not respond to antibiotic treatment.

Chapter 6: Parents’ perceptions of antibiotic use and antibiotic resistance (PAUSE): a qualitative interview study

Unlike routinely collected primary care data, this chapter will give rich insight into parents’ perceptions and understanding of the role of antibiotics when their preschool child has an acute respiratory tract infection, the significance of antibiotic resistance when they consider antibiotics for their child, and strategies they would find acceptable to minimise antibiotic resistance for their children.

Chapter 4 The implications of antibiotic resistance for patients' recovery from common infections in the community: a systematic review and meta-analysis

4.1 Introduction

There are approximately 300 million primary care consultations in the United Kingdom each year (1), for respiratory tract (10-20%) (2), urinary tract (1-3%)(3), and skin and soft tissue infections (1%)(1). Given that almost 75% of all antibiotics in the United Kingdom are prescribed in primary care (see Chapter 2), this is at considerable cost.(4-6)

Chapter 2 also emphasised that antibiotic use in the community is the main driver for carriage of antibiotic-resistant bacteria. There are also major misconceptions about antibiotic resistance which can lead to the perception that failure of antibiotic treatment due to antibiotic resistance has little clinical impact in the community, and remote from every day prescribing decisions.(7, 8) This is a major evidence gap. Chapter 4 will therefore address this by examining the clinical relevance of antibiotic resistance for patients with these common infections in the community.

4.2 Aims and objectives

To assess the impact of antibiotic resistance on clinical outcomes and primary care workload in patients presenting with respiratory tract, urinary tract or skin infections in the community

4.3 Methods

4.3.1 Protocol and registration

The review protocol was registered on the PROSPERO database (CRD42015032441).

4.3.2 Search strategy

A systematic search of MEDLINE (OvidSP), EMBASE (OvidSP), PubMed, Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) and Web of Science Core Databases (Web of Science, Thomson Reuters) was performed from inception to 15 April 2016 with no language restrictions. I used Medical Subject Headings (Mesh) terms and validated search filters for “antibiotic resistance”(9), and “primary care/community setting”(10), and keywords “antibiotic resistance”, “skin or soft tissue infections”, “respiratory tract infections”, “otitis media”, and “urinary tract infections” (Appendix 2). Reference lists of included studies and relevant systematic and narrative reviews were screened and a grey literature search was also performed (<http://www.opengrey.eu/>; <http://www.nyam.org/library/>).

4.3.3 Supplementary search

Studies which collected, but did not publish relevant data were also identified. I wrote to the corresponding authors to request these data, with a reminder sent six weeks later. As a pilot exercise, I contacted the authors of 19 studies (18 RCTs published in 2000 or later) that reported patient-level data on laboratory-confirmed potential pathogens and relevant outcomes to ask whether data on antibiotic resistance were also available. The cut-off of 2000 or later was chosen because we felt it was less likely that studies published less recently would have established whether infections were antibiotic-resistant or not. The authors of seven studies replied, of which one provided additional data reporting outcomes separately for antibiotic-resistant vs sensitive infection.(11) Authors that replied were unable to supply data because data were held at a previous institution (n=1) (12), held by the study sponsor (n=3) (13-15), or the data did not fulfil the inclusion criteria (n=2). (16, 17) Based on these results, I did not proceed to seek additional data from similar studies published before 2000.

4.3.4 Inclusion criteria

Observational studies and randomised controlled trials (RCTs) were eligible for inclusion if the study was conducted in a community setting (general practice, hospital outpatient clinic or emergency department) and reported patient level data on laboratory-confirmed potentially pathogenic infections, antibiotic resistance and clinical outcomes.

Patients of any age presenting with acute respiratory tract, urinary tract, and skin and soft tissue infections were included. I categorised respiratory tract infections (RTI) into community-acquired pneumonia (CAP), sore throat/pharyngitis, acute otitis media (AOM), and acute maxillary sinusitis (AMS). Re-classification was not necessary for urinary tract infections, and skin and soft tissue infections. All bacterial species were considered. Studies had to report data on any of the following outcomes: clinical response failure; re-consultation, further antibiotic prescriptions, symptom duration, and symptom severity.

The primary outcome was clinical response failure which was defined as the persistence of symptoms after completion of antibiotic treatment. Where studies reported outcomes at more than one time point, the time point closest to 7 to 14 days from baseline was selected to reflect the duration of typical antibiotic regimens. Where the outcome was reported as “clinical cure” in the study, I calculated the proportion of patients that had failed to respond to antibiotic treatment within the designated timescale (i.e. 1-proportion of patients with clinical cure). Secondary outcomes were re-consultation, further antibiotic prescriptions (both within 30 days from baseline), symptom duration, and symptom severity.

4.3.5 Exclusion criteria

Studies solely conducted in hospital inpatient settings, involving patients with hospital-acquired infections, and highly-specific patient groups in whom specialised antibiotic treatment strategies are recommended (e.g. cystic fibrosis), were excluded.

4.3.6 Selection procedure

I (OVH) screened all titles, with a second reviewer (KW) reviewing the list of excluded titles to see if any potentially relevant studies had been excluded. Two reviewers (OVH, KW) then independently screened through titles and abstracts. The full text of articles considered as potentially relevant based on title and abstract were independently screened by two reviewers (OVH, KW). Disagreements were resolved by consensus involving a third reviewer (CCB) where necessary.

4.3.7 Data extraction

Two reviewers (OVH, JJJ) independently extracted data on the characteristics of included studies (Table 1). These characteristics included: population demographics, country, type of health care setting, study design, year of study, infection type (i.e. respiratory; urinary tract or skin and soft tissue infection), clinical and laboratory criteria for diagnosis of bacterial infection, bacterial species, antibiotic name and class, total number of patients recruited, definition of antibiotic resistance and outcomes.

For RCTs, outcome data for antibiotic-resistant and antibiotic-sensitive infections were extracted separately for each treatment arm because RCT studies only determined whether infections were antibiotic-resistant or antibiotic-sensitive after patients had already been randomised. Hence randomisation was not stratified according to antibiotic resistance.

Data had to be reported in sufficient detail to assess relevant outcomes between patients with antibiotic-resistant and antibiotic-sensitive infections in order to construct a 2x2 contingency table. Where possible, I extracted outcomes for antibiotic-resistant and antibiotic-sensitive infections whereby resistance and sensitivity were defined in relation to the same antibiotic or class of antibiotic as the antibiotic being prescribed. If studies reported intermediate levels of antibiotic resistance for certain infections, these were classified as antibiotic-resistant infections in

the analysis. If there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed, studies were still included but specifically highlighted.

Where possible, data were extracted on: the total number of laboratory-confirmed infections for *Escherichia coli* (*E. coli*) urinary tract infection (UTI); *Streptococcus pneumoniae* (*S. pneumoniae*) RTI; *Staphylococcus aureus* (*S. aureus*) skin and soft tissue infection, the number of these infections which were defined as being antibiotic-resistant based on the laboratory criteria specified in the study, and the proportion of patients with these resistant infections that were associated with clinical response failure.

4.3.8 Risk of bias assessment

The quality of the included studies was assessed independently by two reviewers (OVH, JJJ) for RCTs and observational studies based on their respective risk of bias tool, namely the Cochrane Collaboration's tool for assessing risk of bias in randomised trials and the critical appraisal skills programme (CASP) checklist for cohort studies (Appendices 3 and 4).^(18, 19) Study quality was reported *a priori* because it was anticipated that the primary aim of examining the impact of antibiotic resistance on patient outcomes in community settings was likely not the primary objective of the original study. For this reason, I did not use quality measures to determine studies for sensitivity analyses.

4.3.9 Statistical analysis

To compare the likelihood of clinical response failure between antibiotic-resistant and antibiotic-sensitive infections, I calculated odds ratios (OR) with 95% confidence intervals (CI) for infections where data were available from three or more studies for the same bacterial pathogen using random effects meta-analysis.

Random effects meta-analysis was pre-specified in recognition of clinical diversity between studies. I considered performing meta-analysis of only two studies. However, I decided against this because estimating the between-studies variance without sufficient numbers of studies in a random effects model is potentially problematic.(20) Thus, I combined data from a minimum of three of more different studies to estimate the common effect or impact of antibiotic resistance.

Heterogeneity was assessed using the chi-squared test and I^2 statistic. ORs in relation to re-consultation and further antibiotic prescriptions were calculated using similar methods as those used for clinical response failure. For continuous data, I planned to plot survival curves where possible for duration and severity of symptoms in antibiotic-resistant versus antibiotic-sensitive infections.

Subgroup analyses were performed according to study design (observational studies vs RCTs) and type of health care setting (general practice, hospital outpatient clinic, or emergency department). Results were summarised narratively where data were not sufficient to perform meta-analysis or plot survival curves. Analysis was conducted using StataSE version 13.

Table 1 Characteristics of 26 included studies (primary and/or secondary outcomes) according to infection

Study	Country	Setting	Infection type	Study design	Participants	Potential pathogen being studied	Total number recruited	Total number with potential pathogen being studied	Number of potential pathogens being studied with evidence of antibiotic resistance	Number of patients where resistance and outcome data available	Primary Outcome time point † §	Secondary outcomes ±	Treatment antibiotic/antibiotic class ¹	Antibiotic to which resistance measured
Urinary tract infection (UTI)														
Brown et al. (2002)(21)	USA	OP/PHC	UTI	Obs (R)	Wo	E	NR	601 isolates §	44	104	-	Rec ±	TMP-SMX	TMP-SMX
Butler et al. (2006)(11)	United Kingdom	PHC	UTI	CC Obs (P)	Adu	E	932	922	94	797¹ 862 (Rec)² 816 (Fab)² 420 (Sdur)²	within 30 days	Rec ± Fab ± Sdur ±	Not specified	To prescribed antibiotic¹ To at least one antibiotic²
Gupta et al. (2007)(22)	USA	PHC	UTI	RCT	Wo	E	338	276	34	308 **	Day 3 §	-	TMP-SMX Nitrofurantoin	TMP-SMX Nitrofurantoin
Little et al. (2010)(23)	United Kingdom	PHC	UTI	Obs (P)	Wo	NR ^d	843	NR	NR	264 (Sdur) 264 (Ssev)	-	Sdur ± Ssev ±	Not specified	To one or more antibiotics
McNulty et al. (2006)(24)	United Kingdom	PHC	UTI	Obs (P)	Wo	E	497	298 ^b	44	207 (Sdur)** 317 (Rec)	Day 7 §	Sdur ± Rec ±	Trimethoprim	Trimethoprim
Noskin et al. (2001)(25)	USA	OP	UTI	Obs (P)	Wo	E	156	89	42	71	NR §	-	Not specified	To one or more antibiotics
Raz et al. (2002)(26)	Israel	OP	UTI	Obs (P)	Wo	E	618	425	30	484 **	Day 5-9 §	-	TMP-SMX	TMP-SMX
Soraas et al. (2014)(27)	Norway	Other	UTI	Obs (P)	Adu	ESBL-E	343	343 §	81 (ESBL-E)	343	within 14 days §	Fab ±	Mecillinam Non-mecillinam	Mecillinam and ESBL status
Vallano et al. (2006)(28)	Spain	PHC	UTI	Obs (P)	Wo	E	220	88	15 **	108 **	within 14 days §	-	Not specified	To one or more antibiotics
Van Merode et al. (2005)(29)	Netherlands	PHC	UTI	RCT	Wo	E	324	80	17	114 **	Day 6-8 §	-	Trimethoprim	Trimethoprim
Community-acquired pneumonia (CAP)														
Cao et al. (2010)(30)	China	OP	RTI (CAP)	Obs (P)	Adu; Adol	MP	356	67	46	59	-	Fab ± Sdur ±	Not specified	Erythromycin
Hagberg et al. (2003)(31)	Multiple	IP/OP	RTI (CAP)	Pooled data from 6 phase III trials	Adu	SP	1,373	174	23 ^c	174	Day 3-5 §	-	Telithromycin	Penicillin or erythromycin
Kawai et al. (2012)(32)	Japan	OP	RTI (CAP)	Obs (P)	Chi; Adol	MP	476	50	21	30	-	Fab ±	Not specified	To one or more macrolide
O'Doherty et al. (1997)(33)	United Kingdom; Ireland	OP	RTI (CAP)	RCT	Adu	SP	264	30 ^e	6	30	Day 3-5 §	-	Grepafloxacin Amoxicillin	Amoxicillin
Van Rensburg et al. (2005)(34)	Multiple	OP	RTI (CAP)	Pooled RCT (8 phase III trials and 1 phase II study)	Adu	SP	2339	418	61	327	Day 17-24 §	-	Telithromycin	To erythromycin and penicillin
Yanagihara et al. (2004)(35)	Japan	OP	RTI (CAP)	Obs (R)	Adu	SP	306	306	129	306	NR §	-	Not specified	Penicillin
Zhan et al. (2014)(36)	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adu; Chi	SP	872 ^h CAP 309	CAP 79	CAP 27	CAP 79	NR §	-	Azithromycin	Azithromycin

Acute otitis media (AOM)														
Barry et al. (1994)(37)	France	OP	RTI (AOM)	Pooled data from 3 RCTs	Chi	SP	1,092	236	54 ^a	219	Day 10	-	B-lactams (combined)	Penicillin; B-lactams
Dagan et al. (1996)(38)	Israel	ER	RTI (AOM)	RCT	Chi	SP	266	98	18	77	Day 10	-	Cefuroxime Cefaclor	Cefuroxime Cefaclor
Hoberman et al. (1996)(39)	Multiple	IP/OP	RTI (AOM)	Obs (P)	Chi	SP	917	298	82	260	Day 12-14 [§]	-	Co-amoxiclav	Penicillin
Hoberman et al. (2005)(40)	Multiple	OP	RTI (AOM)	RCT	Chi	SP	730	229	158	188	Day 12-14 [§]	-	Co-amoxiclav Azithromycin	Penicillin Azithromycin
Zhanel et al. (2014)(36)	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adu; Chi	SP	872 ^b AOM 402	AOM 177	AOM 41	AOM 177	NR	-	Azithromycin	Azithromycin
Acute sore throat														
Quinn et al. (2003)(41)	USA; Canada	OP	RTI (sore throat)	RCT	Adu; Adol	SPy	526	360 ^t	9	285	Day 16-23 [§]	-	Telithromycin Clarithromycin	Erythromycin
Seppala et al. (2002)(42)	Finland	OP	RTI (sore throat)	Obs (R)	NR	SPy	NR	529	76	273	NR	-	Erythromycin Penicillin	Erythromycin
Acute maxillary sinusitis (AMS)														
Buchanan et al. (2005)(43)	Sweden	Other	RTI (AMS)	Pooled data from 3 RCTs	Adu; Adol	SP	1,298	126	1	78	Day 17-24 [§]	-	Telithromycin	Telithromycin
Zhanel et al. (2014)(36)	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adu; Chi	SP	872 ^b AMS 161	AMS 57	AMS 19	AMS 57	NR	-	Azithromycin	Azithromycin
Skin and soft tissue infection														
Dagan et al. (1992)(44)	Israel	OP	Skin (Imp)	RCT	Chi	SA	102	90	27	89	Day 3-8	-	Erythromycin Mupirocin	Erythromycin, Mupirocin
Giordano et al. (2006)(45)	USA	Other	Skin (USSSI)	RCT	Adu; Adol	SA	392	171	79	151	Day 17-24 [§]	-	Cefdinir Cephalexin	Methicillin
Overall							15,580			5,659 ³				

[†] Primary outcome: “response failure” defined as the persistence of symptoms after completion of antibiotic treatment. Where the outcome was reported as “clinical cure” in the study, the proportion of patients that had failed to respond to antibiotic treatment within the designated timescale (i.e. 1-proportion of patients with clinical cure) was calculated. [§] Data on clinical cure, rather than clinical response failure, were reported by ten RCTs (22, 29, 31, 33, 34, 36, 40, 41, 43, 45), and seven observational studies.(24-28, 35, 39) Overall, clinical response failure was assessed between 3-5 days from baseline in three studies (22, 31, 33), between 6-10 days in six studies (24, 26, 29, 37, 38, 44), between 11-14 in four studies (27, 28, 39, 40), between 20-30 days in five studies (11, 34, 41, 43, 45), and not reported in four studies.(25, 35, 36, 42)

[‡] Secondary outcomes: re-consultation (Rec), further antibiotic prescriptions (Fab), symptom duration (Sdur) and symptom severity (Ssev). [§] we assumed one isolate per participant.

^aMultiple antibiotics prescribed in separate study arms

OP: Hospital outpatients. PHC: primary care clinic/general practice. UTI: Urinary tract infections. Obs (R): Retrospective observational. Wo: women. *E. coli*. NR: not reported. TMP-SMX: Trimethoprim-sulfamethoxazole. CC: case control. Obs (P): Prospective observational. Adu: Adults. RCT: Randomised controlled trial. Other: community setting (not specified). ESBL-*E. coli*. ** all combined pathogens. Other: Other community setting. RTI: Respiratory tract infection. CAP: community-acquired pneumonia. Adol: adolescents. *MP: M. pneumoniae*. *IP: Hospital inpatients*. *SP: S.*

pneumoniae. Chi: Children. AMS: acute maxillary sinusitis. AOM: acute otitis media. ER: Emergency room. *Spy*: *S. pyogenes*. Imp: impetigo. SA: *S. aureus*. USSSI: *uncomplicated skin and skin structure infections (e.g. cellulitis, erysipelas, impetigo, simple abscess, wound infection, furunculosis, folliculitis)*.

a: One child in the SpRP group did not complete the treatment course because of adverse events and was not evaluable for clinical response. b: Coliforms; 242 single isolates were sent to HPA Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) of which *E.coli* accounted for 90% (219/242). c: Penicillin or erythromycin-resistant (all *S.pneumoniae* isolates were susceptible to telithromycin). d: Specific organism not reported. e: Only 81 were evaluated microbiologically. f: positive screening for Group A β -haemolytic streptococcus. g: ESBL-*E. coli* and non-ESBL-*E. coli* only. h: excluded acute exacerbations of chronic bronchitis. -: not applicable. ¹: Resistance measured to prescribed antibiotic; ²: Resistance measures to at least one antibiotic; ³: where more than one outcome data available, the lowest number was taken

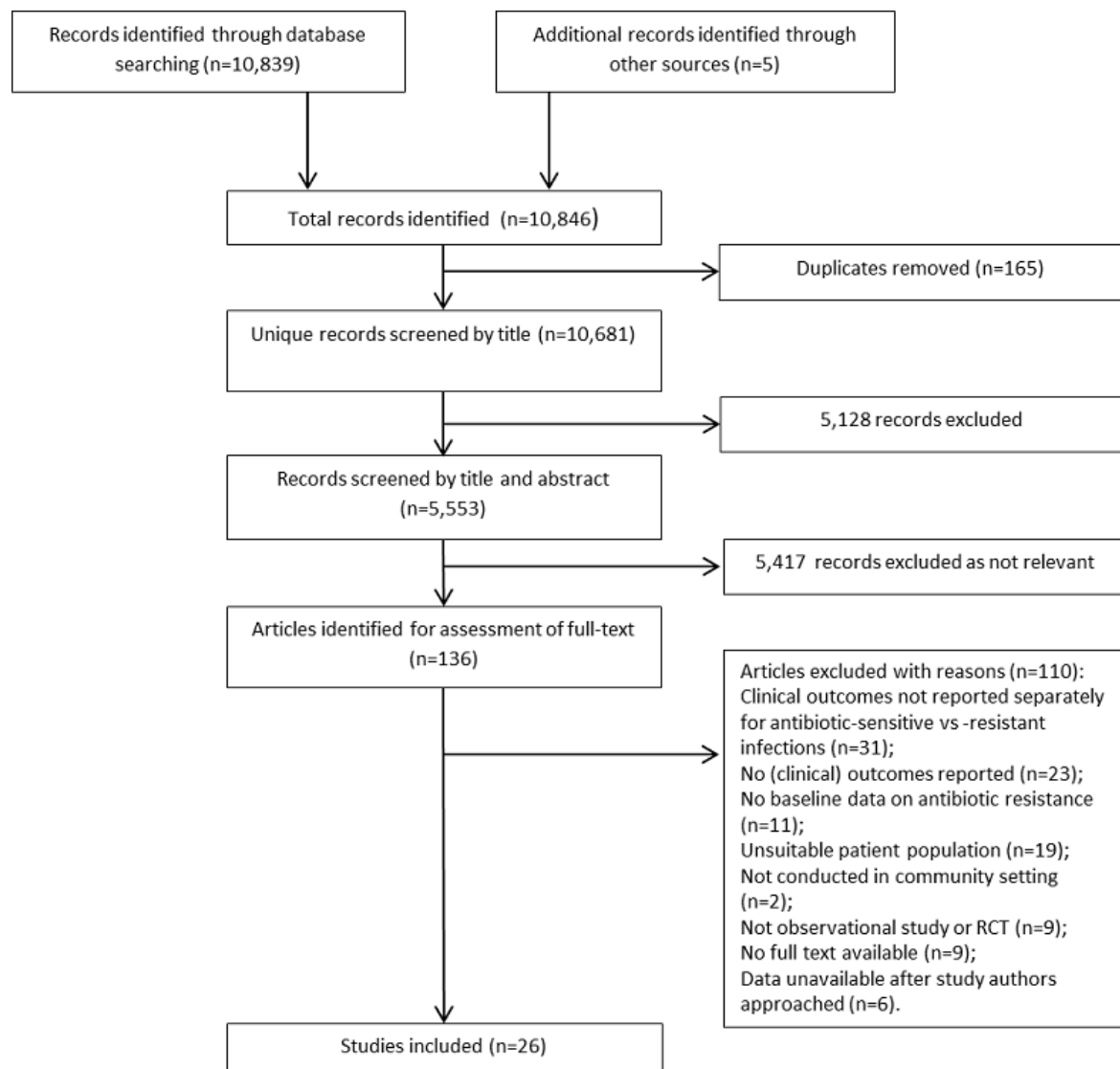
4.4 Results

4.4.1 Study selection

We identified 10,681 records of which 136 full-text articles were assessed (Fig 1). The most common reason for exclusion ($n=31/107$) was that clinical outcomes were not reported separately for antibiotic-resistant versus antibiotic-sensitive infections.

Figure 1 Study selection

(Permission to reproduce this figure has been granted by Oxford University Press.)



4.4.2 Study characteristics

Twenty-six studies were included (Fig 1; Table 1), of which 13 were observational studies, eight were RCTs and five were secondary analyses of pooled RCT data.(31, 34, 36, 37, 43) Six studies were conducted in primary care/general practice, 12 in hospital outpatients, one in a mixed outpatient/primary care setting, two in a mixed outpatient/inpatient setting, one in an emergency department setting, and four in another community setting which was not clearly defined. Our included RCTs and secondary analyses did not report any duplicate data. Of the included studies, only three studies had as their primary objective the association between antibiotic resistance and patient outcomes.(11, 23, 24)

Data relating to one or more study outcomes were available for 15,580 patients of whom 6,617 patients had a laboratory-confirmed potentially pathogenic bacterial infection. Data on whether the infection was antibiotic-resistant or antibiotic-sensitive were also available for 5,659 of these patients (antibiotic-resistant: n=1,268; antibiotic-sensitive: n=4,391; Table 2).

Table 2 Data related to one or more study outcomes according to infection type and bacterial pathogen

Infection	Bacteria	Number of studies	Number of antibiotic-resistant infections	Number of antibiotic-sensitive infections
UTI	<i>E. coli</i>	10	523	2, 277
CAP	<i>S. pneumoniae</i>	5	246	670
CAP	<i>M. pneumoniae</i>	2	63	24
AOM	<i>S. pneumoniae</i>	5	225	696
Sore throat	Group A β -haemolytic Streptococcus	2	85	473
AMS	<i>S. pneumoniae</i>	2	20	115
Skin infection	<i>S. aureus</i>	2	106	134

UTI: urinary tract infection; *E. coli*: Escherichia coli; CAP: community-acquired pneumonia; *S. pneumoniae*: Streptococcus pneumoniae; *M. pneumoniae*: Mycoplasma pneumoniae; AOM: acute otitis media; AMS: acute maxillary sinusitis; *S. aureus*: Staphylococcus aureus

Ten studies reported data on participants with *E. coli* UTI (antibiotic resistant, n=523; antibiotic-sensitive, n=2,277) (11, 21-29), five studies on *S. pneumoniae* CAP (antibiotic-resistant, n= 246; antibiotic-sensitive, n=670) (31, 33-36), two studies on *M. pneumoniae* (antibiotic-resistant, n=

63; antibiotic-sensitive, n=24) (30, 32), five studies on *S. pneumoniae* AOM (antibiotic-resistant, n=225 ; antibiotic-sensitive, n=696) (36-40), two studies on Group A β -haemolytic Streptococcus sore throat (antibiotic-resistant, n= 85; antibiotic-sensitive, n=473) (41, 42), two studies on *S. pneumoniae* AMS (antibiotic-resistant, n= 20 ; antibiotic-sensitive, n= 115) (36, 43), and two studies on *S. aureus* skin infection (antibiotic-resistant, n= 106 ; antibiotic-sensitive, n= 134.(44, 45)

Clinical criteria for obtaining urine samples and diagnosing urinary tract infections varied between studies. Diagnostic thresholds used to define *E. coli* UTIs were reported as being $>10^4$ colony forming units (CFU) in three studies (Appendix 5).(24, 25, 27) Four studies obtained urine samples from patients with urinary symptoms and positive urine dipstick test (21, 24-26), two studies obtained urine samples from patients with urinary symptoms only (22, 29), one study obtained urine samples from patients with “clinically suspected” UTI (11), and two studies did not report selection criteria for obtaining urine samples. (27, 28) Most UTI studies counted infections of mixed uropathogens as indicating an infection, however the dominant bacterium ($>65\%$) was *E. coli* in all UTI studies. Where calculations were possible, the proportion of clinically suspected UTIs that had a laboratory confirmed infection was between 57-95%.

Three studies based clinical diagnosis of *S. pneumoniae* CAP on symptoms, radiographic evidence and blood tests (31, 33, 35), one study based diagnosis on symptoms (34), and one study (36) did not report how a diagnosis was established (Appendix 6). Diagnostic criteria for *S. pneumoniae* CAP and AOM (Appendices 6 and 7) were more uniform (symptoms, examination, and tympanocentesis) except for one study for which this was not reported.(36)

Data relating to the primary outcome (clinical response failure) were available from 13 RCTs (22, 29, 31, 33, 34, 36-38, 40, 41, 43-45), and nine observational studies.(11, 24-28, 35, 39, 42)

Clinical response failure was assessed between 3-5 days from baseline in three studies (22, 31, 33), between 6-10 days in six studies (24, 26, 29, 37, 38, 44), between 11-14 days in four studies

(27, 28, 39, 40), between 20-30 days in five studies (11, 34, 41, 43, 45), and not reported in four studies.(25, 35, 36, 42)

Three observational studies reported data on re-consultations (11, 21, 24); four studies reported data for further antibiotic prescriptions (11, 23, 27, 30); four studies reported data for symptom duration (11, 23, 24, 30) and one study reported data on symptom severity.(23) Data on these outcomes were not reported by any RCTs or secondary analyses of pooled RCT data.

Appendices 3 and 4 summarises the risk of bias assessment of included studies. For 12 of 13 RCTs, there was low risk of reporting bias.(22, 29, 31, 33, 36-38, 40, 41, 43-45) Only one RCT reported assessing outcomes blinded from knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive.(38) We were not able to assess whether RCTs considered confounding variables between antibiotic-resistant and antibiotic-sensitive infections except for one RCT (38), because baseline characteristics of the study population were not reported according to whether participants had an antibiotic-resistant or antibiotic-sensitive infection.

For the 13 observational studies, participants were representative of the defined population except for one study (27), and generally clearly defined. Antibiotic exposure was accurately measured (e.g. secure medical records) in ten studies.(3, 18, 19, 22-25, 28, 29, 35) Only six observational studies attempted to address potential confounders (3, 18-20, 24, 30), and measurement of outcome was only satisfactorily blinded in two studies.(11, 21)

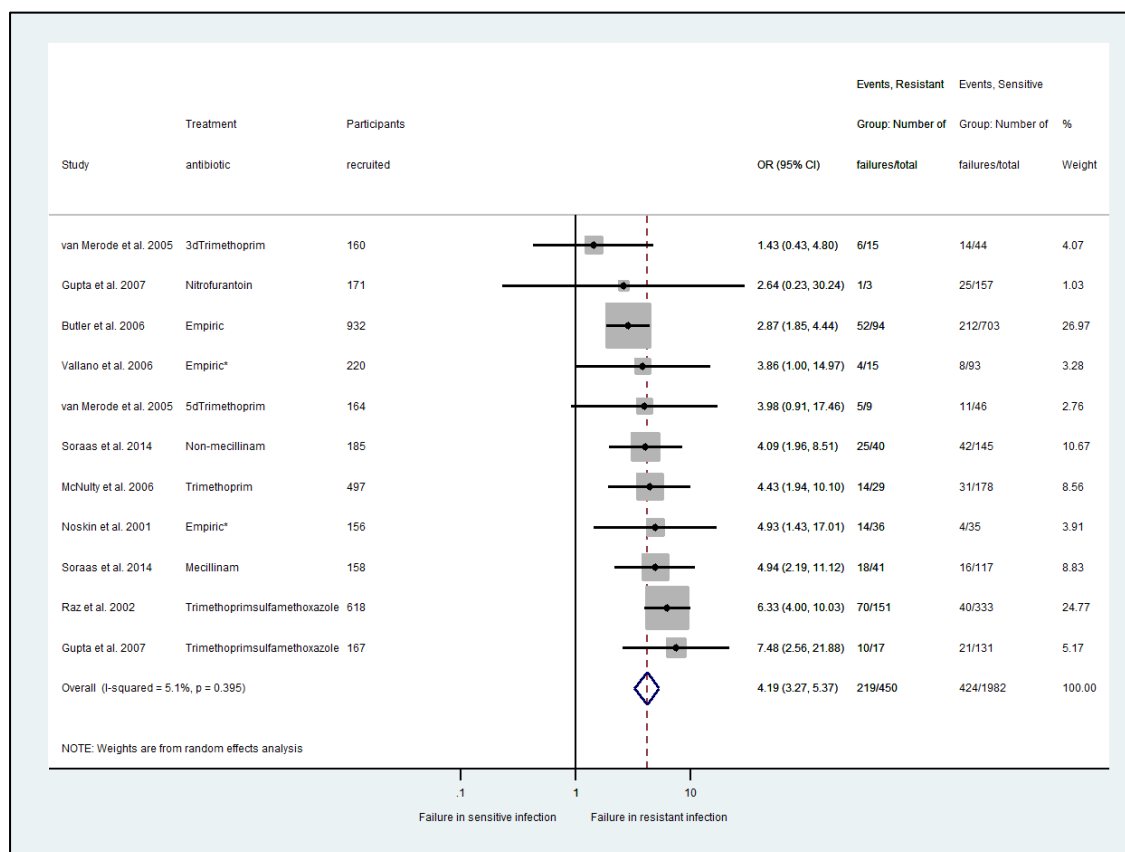
4.4.3 Primary outcome

Figures 2 to 4 summarise odds ratios with 95% confidence intervals for participants with antibiotic-resistant *E. coli* UTIs (Figure 2), *S. pneumoniae* CAP (Figure 3) and *S. pneumoniae* AOM (Figure 4) in relation to clinical response failure.

Clinical response failure was significantly more likely in antibiotic-resistant than antibiotic-sensitive *E. coli* UTIs (Fig. 2, OR 4.19 [95%CI 3.27–5.37]; n = 2,432 participants, eight studies).(11, 22, 24-29)

Figure 2 Comparison between antibiotic-resistant and antibiotic-sensitive (*E. coli*) urinary tract infections in relation to clinical response failure

(Permission to reproduce this figure has been granted by Oxford University Press)



Odd ratio (OR) more than 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection. *: indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed.

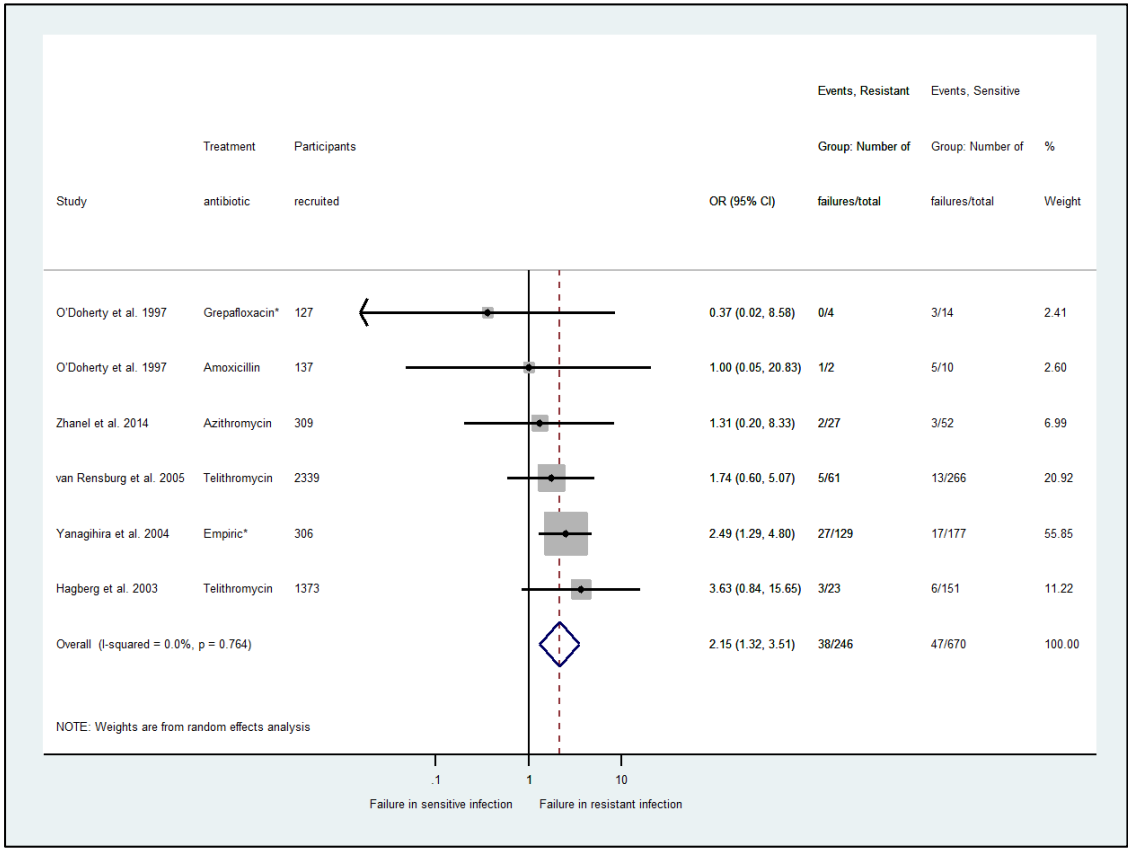
Antibiotic-resistant *S. pneumoniae* CAP and AOM were also associated with significantly greater odds of clinical response failure respectively (CAP: Fig. 3, OR 2.15 [95%CI 1.32–3.51]; 916 participants, five studies (31, 33–36); AOM: Fig.4, OR 2.51 [95%CI 1.29–4.88]; 921 participants, five studies).(36–40)

Clinical heterogeneity precluded meta-analysis for skin infections, because data were only available from two studies (44, 45), of which one study involved children with impetigo and the other study involved adults and adolescents with a range of different infections, including cellulitis, simple abscesses and wound infections. Likewise for sore throat, there was uncertainty regarding similarity of study population characteristics between the two studies (41, 42), and for

sinus infections.(36, 43) One study (43) had only one patient with an antibiotic-resistant infection (Appendices 8-10).

Figure 3 Comparison between antibiotic-resistant and antibiotic-sensitive (*S. pneumoniae*) community-acquired pneumonia in relation to clinical response failure

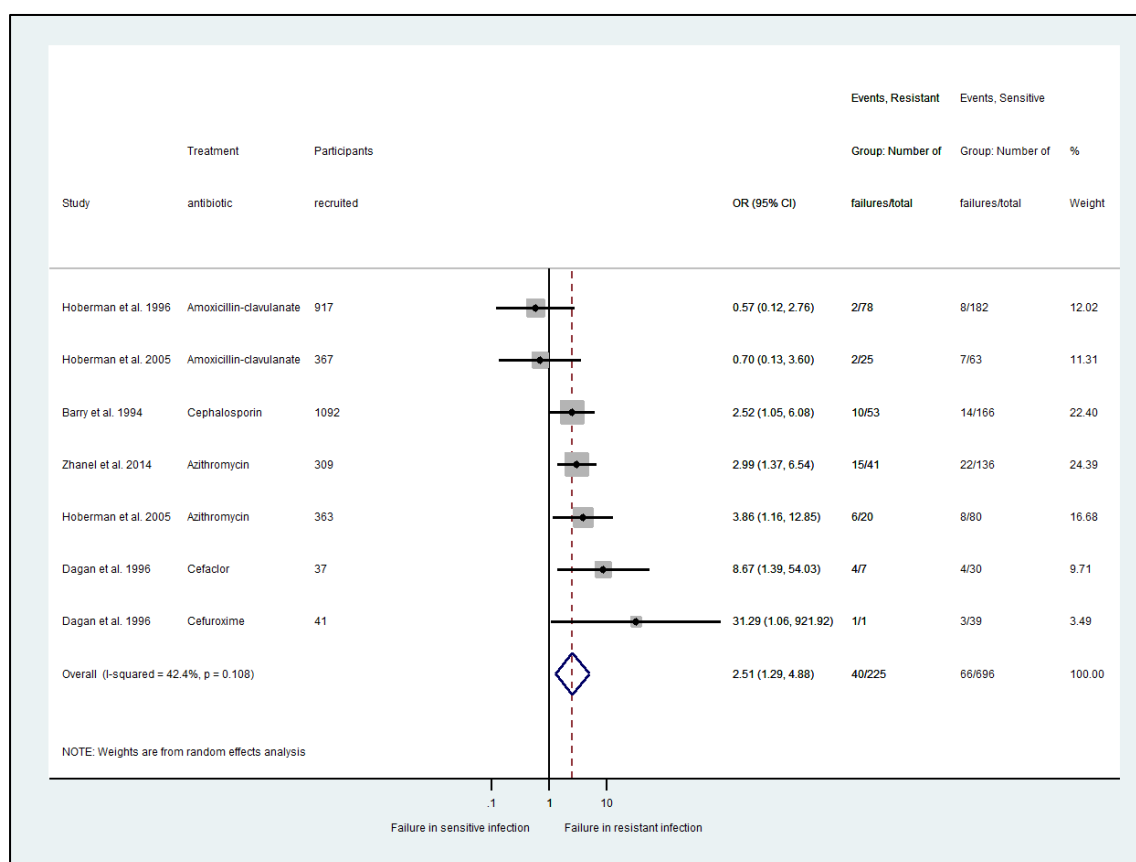
(Permission to reproduce this figure has been granted by Oxford University Press)



Odd ratio (OR) more than 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection; *: indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed.

Figure 4 Comparison between antibiotic-resistant and antibiotic-sensitive (*S. pneumoniae*) acute otitis media in relation to clinical response failure

(Permission to reproduce this figure has been granted by Oxford University Press)



Odd ratio (OR) more than 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection; *, indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed.

4.4.4 Secondary outcomes

Re-consultation was significantly more likely in patients with antibiotic-resistant *E. coli* UTIs (Appendix 11), OR 5.07 [95%CI 2.17–11.82]; n=1,283 participants; three studies).(11, 21, 24)

Data on patient re-consultations were not available for other types of infection. Two studies involving patients with *M. pneumoniae* CAP reported data on further antibiotic prescriptions (Appendix 12).(30, 32) However, meta-analysis was not performed because one study did not report which antibiotic was used to treat patients (30), and there were no outcome events among patients with antibiotic-sensitive infections in the other study.(32) Two studies involving patients with *E. coli* UTIs also reported data on further antibiotic prescriptions.(11, 27) However,

treatment antibiotic was not reported in one study (11), and the other study focused specifically on extended-spectrum beta-lactamases (ESBL) *E. coli* infections.(27) Antibiotic-resistant infections were associated with longer duration of symptoms in two (23, 24) of three *E. coli* UTI studies (11, 23, 24), but not in the one *M. pneumoniae* CAP study (Table 3).(30)

Table 3 Symptom duration between antibiotic-resistant and antibiotic-sensitive infections

Study	Total number of patients	Time period	Infection type	Treatment antibiotic	Symptom duration (days) in resistant group, mean (SD) or median (IQR)	Symptom duration (days) in sensitive group, mean (SD) or median (IQR)	P-value
Cao et al. 2010	59	48-72h	<i>M. pneumoniae</i> CAP	Empiric**	10 mean (8-14)	8 mean (6-12)	0.11
Butler et al. 2006	816	30 days	<i>E. coli</i> UTI	Empiric*	7 median (3-17)	5 median (3-12)	0.12
Little et al. 2010	264	14 days	<i>E. coli</i> UTI	Empiric*	4.73 mean (2.91)	3.32 mean (2.54)	0.001 [§]
McNulty et al. 2006	207	10 days	<i>E. coli</i> UTI	Trimethoprim	7 median (6.9) [†]	4 median (4.6) [†]	0.0002

SD: standard deviation; IQR: interquartile range; ** resistant to erythromycin; * resistant to one or more antibiotics; [§] multivariate analysis (age leaving full time education, marital status, number of medical problems, previous duration of symptoms, and perception of doctor communication and health anxiety (Whitley index)). [†] single value rather than range reported

Only one study (Table 4) compared symptom severity between antibiotic-resistant and antibiotic-sensitive *E. coli* UTIs and found that patients with resistant infections had significantly greater symptom severity between days 2 and 4 (antibiotic-resistant 2.01, standard deviation (0.89) versus antibiotic-sensitive 1.47, SD (0.88); $p < 0.001$, 264 participants; severity grading 0 = no symptoms, 6 = as bad as it could be).(23)

Table 4 Symptom severity* between antibiotic-resistant and antibiotic-sensitive urine infections

Study	N total (evaluable)	Time elapsed	Infection type	Treatment antibiotic	Resistant group	Sensitive group
Little 2010	264	Days 2-4	<i>E. coli</i> UTI	Not specified	2.01 (mean) [†] SD [0.89]	1.47 (mean) SD [0.88]

*Severity of symptoms in "frequency group" at days 2 to 4 (increased day frequency, increased night frequency, and urgency and dysuria); Severity graded grading for up to 14 days: 0 (no symptoms), 1 (very slight problem), 2 (slight problem), 3 (moderately bad problem), 4 (bad problem), 5 (very bad problem), or 6 (as bad as it could be). [†] Adjusted multivariate analysis

4.4.5 Subgroup analysis

Increased odds of clinical response failure in antibiotic-resistant *E. coli* UTIs were demonstrated in both observational studies (OR 4.28 [95%CI 3.31–5.54]) and RCTs (OR 3.49 [95%CI 1.53–7.97]). Odds of clinical response failure were also increased among participants recruited from both hospital outpatient (5.42 [3.87–7.61]) and primary care settings (3.29 [2.38–4.56]).

4.4.6 Sensitivity analysis

For *E. coli* UTIs, post hoc sensitivity analysis was conducted excluding studies conducted in areas where the prevalence of antibiotic-resistant infections was reported to be high (26), studies which examined highly-specific antibiotic-resistant bacteria (e.g. ESBL-*E. coli*) (27), studies where the reported susceptibility did not match the treatment antibiotic class (31, 33–35), and studies where the treatment antibiotic was not specified.(25, 28) This did not change the overall findings for clinical response failure (OR 3.27 [95%CI 2.32–4.60]; 1,426 participants, four studies).(11, 22, 24, 29)

For *S. pneumoniae* CAP, the findings were no longer statistically significant (OR 1.22 [95%CI 0.25–5.91]; 91 participants, two studies) (33, 36), after excluding studies where the reported susceptibility did not match the prescribed treatment antibiotic class (31, 34), or where the treatment antibiotic was not reported.(35) For *S. pneumoniae* AOM, the overall findings did not change (OR 3.37 [95%CI 2.04–5.56]; 573 participants, four studies) (36–38, 40), after excluding one study conducted in an inpatient/outpatient setting.(39)

4.5 Discussion

4.5.1 Main findings

The findings demonstrate that patients who present in community health care settings with antibiotic-resistant urinary tract and respiratory tract infections are more likely to experience clinical response failures than patients with antibiotic-sensitive infections. Patients with

antibiotic-resistant *E. coli* UTIs are also more likely to re-consult a health care professional and experience prolonged and more severe symptoms than patients with antibiotic-sensitive infections. This challenges the perception that patients in the community are at little additional personal risk from the impact of antibiotic resistance for common infections.

4.5.2 Strengths and limitations

4.5.2.1. Strengths

Several widely cited reviews have been done on the rather limited question of the association between antibiotic use and microbiological outcomes (e.g. Costelloe *BMJ* 2010, cited 414 times, Web of Science).(9, 46) However, the clinical relevance of antibiotic resistance for common infections is of far greater relevance to patients and clinicians in the community, moving beyond a laboratory-focused, microbiological outcome. This world-first, and rigorous systematic review and meta-analysis, brings us a step closer to filling this major gap in the evidence by assessing the implications of antibiotic resistance for patient recovery from the three commonest infections in the community.

The search strategy was comprehensive and used validated search filters. Both RCTs and observational studies conducted in community health care settings were included. There were no language restrictions. We identified studies which may have collected but did not publish relevant data, and I contacted a sample of the authors to request unpublished and/or additional data.

Since most of the included studies specifically excluded patients with known medical conditions (11, 21-30, 33, 34, 37, 39-45), the impact of antibiotic-resistant infections in patients with multimorbidity may be underestimated. Individual patient data were not available to allow adjustment for potential confounders.

4.5.2.2. Limitations

An important limitation is that antibiotic resistance is just one explanation for clinical response failure, which could also be due to factors such as co-infection or re-infection. It is not possible to say what the relative contribution of antibiotic resistance was compared to other factors which could potentially influence the likelihood of clinical response failure. Such factors may also explain why a significant proportion of patients with sensitive infections failed to respond to antibiotics. Previous studies of failure from antibiotic treatment have been criticised because many patients probably had viral infections and would not have been expected to recover because of antibiotic treatment.(47) All included patients in our review had laboratory-confirmed bacterial infections. That said, this may limit generalisability of findings to clinical practice, given that treatment decisions in the community are based on clinical findings without knowledge of the causative pathogen, and where most respiratory infections, for example, are viral.

Published data were restricted to common but specific bacteria. This is important to bear in mind as the role of antibiotic use in driving the emergence of resistance is likely to be specific to each drug and to each organism (Chapter 2), as will be the effect of changes in antibiotic use. This means the ability of bacteria to cross-select and co-select resistance determinants is not taken into account when looking at just one pathogenic bacteria.

Clinical criteria for diagnosing infections varied between studies which could impact on clinical outcome. This was particularly evident for *E. coli* UTIs where criteria for obtaining urine samples and diagnostic thresholds varied. Using a lower reference standard of $\geq 10^2$ CFU/ml and of $\geq 10^3$ CFU/ml, and combining nitrite dipstick test results with clinical symptoms and signs improves diagnostic accuracy for UTI (48), and therefore earlier treatment initiation and improved outcome.(49)

Although I applied a consistent approach associating resistance and sensitivity data to a specific antibiotic class, the class of treatment antibiotic was not always consistent with the class of antibiotic against which resistance was measured. This potentially overestimates clinical response

failure associated with resistance to the specific antibiotic being used for treatment. Clinical response failures were more likely in both the main analysis and sensitivity analysis for *E. coli* UTIs and *S. pneumoniae* AOM but not sustained for the sensitivity analysis for *S. pneumoniae* CAP. Therefore it is not possible to reach a robust conclusion that there was no greater likelihood of failure in resistant *S. pneumoniae* CAP compared to sensitive *S. pneumoniae*. Potential reasons for this may be the limited number of participants with CAP (n=91), the low number of outcome events overall (n=11), or that clinical criteria for CAP diagnosis were not reported in one of the two studies.(36) Data were limited for some infections (e.g. skin and soft tissue infection) and secondary outcomes. It remains unclear if other infections or bacteria have similar implications on patients' illness burden.

4.5.3 Conclusions

Antibiotic resistance has worse implications for patients' illness burden in the community – even for common infections. These findings could usefully inform better dialogue between clinician and patient, guidelines and campaigns about the benefits and risks of antibiotic treatment, and reduce unnecessary antibiotic use for self-limiting infections.

A subset of the population that is at particular risk of receiving antibiotics unnecessarily is preschool children. Using routinely collected primary care data, Chapter 5 will examine the implications of antibiotic use in preschool children by exploring whether preschool children exposed to more antibiotics are more likely to get subsequent respiratory tract infections that do not respond to antibiotic treatment.

4.6 References

1. Hippisley-Cox J, Vinogradova Y. Trends in consultation rates in General Practice 1995/1996 to 2008/2009: Analysis of the QResearch® database. Final report to the NHS Information Centre and Department of health. Leeds, UK: The NHS Information Centre for health and social care; 2009.
2. Ashworth M, Latinovic R, Charlton J, Cox K, Rowlands G, Gulliford M. Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using

- the General Practice Research Database. *Journal of public health (Oxford, England)*. 2004;26(3):268-74.
3. MeReC. Urinary tract infection. *MeReC Bulletin*. 1995;6(8):1-7.
 4. Cals JW, Ament AJ, Hood K, Butler CC, Hopstaken RM, Wassink GF, et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *Journal of evaluation in clinical practice*. 2011;17(6):1059-69.
 5. Hollinghurst S, Gorst C, Fahey T, Hay AD. Measuring the financial burden of acute cough in pre-school children: a cost of illness study. *BMC family practice*. 2008;9:10.
 6. Rosenberg M. Pharmacoeconomics of treating uncomplicated urinary tract infections. *International journal of antimicrobial agents*. 1999;11(3-4):247-51; discussion 61-4.
 7. Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2015;65(639):e702-7.
 8. Wood F, Simpson S, Butler CC. Socially responsible antibiotic choices in primary care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluoroquinolone antibiotics. *Family practice*. 2007;24(5):427-34.
 9. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2010;340:c2096.
 10. Gill PJ, Roberts NW, Wang KY, Heneghan C. Development of a search filter for identifying studies completed in primary care. *Family practice*. 2014;31(6):739-45.
 11. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with *E. coli* UTIs. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2006;56(530):686-92.
 12. Bjerrum L, Gahrn-Hansen B, Grinsted P. Pivmecillinam versus sulfamethizole for short-term treatment of uncomplicated acute cystitis in general practice: a randomized controlled trial. *Scandinavian journal of primary health care*. 2009;27(1):6-11.
 13. Arredondo-Garcia JL, Figueroa-Damian R, Rosas A, Jauregui A, Corral M, Costa A, et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. *The Journal of antimicrobial chemotherapy*. 2004;54(4):840-3.
 14. Desrosiers M, Ferguson B, Klossek JM, Drugeon H, Mosges R. Clinical efficacy and time to symptom resolution of 5-day telithromycin versus 10-day amoxicillin-clavulanate in the treatment of acute bacterial sinusitis. *Current medical research and opinion*. 2008;24(6):1691-702.
 15. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. *The Journal of antimicrobial chemotherapy*. 2004;54(2):515-23.
 16. Monsen TJ, Holm SE, Ferry BM, Ferry SA. Mecillinam resistance and outcome of pivmecillinam treatment in uncomplicated lower urinary tract infection in women. *APMIS : acta pathologica, microbiologica, et immunologica Scandinavica*. 2014;122(4):317-23.
 17. Syrogiannopoulos GA, Bozdogan B, Grivea IN, Ednie LM, Kritikou DI, Katopodis GD, et al. Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *The Pediatric infectious disease journal*. 2004;23(9):857-65.
 18. Cochrane Collaboration. Cochrane Risk of Bias Assessment Tools for Randomised Controlled Trials In: Higgins JPT, Green S, editors. in *Cochrane handbook for systematic reviews of interventions* 2011.
 19. Critical Appraisals Skills Programme (CASP). CASP Checklists Oxford2013 [Available from: <http://www.casp-uk.net/>].

20. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. When Does it Make Sense to Perform a Meta-Analysis? *Introduction to Meta-Analysis*. Chichester: John Wiley & Sons, Ltd.; 2009. p. 357-64.
21. Brown PD, Freeman A, Foxman B. Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2002;34(8):1061-6.
22. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Archives of internal medicine*. 2007;167(20):2207-12.
23. Little P, Merriman R, Turner S, Rumsby K, Warner G, Lowes JA, et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. *BMJ (Clinical research ed)*. 2010;340:b5633.
24. McNulty CA, Richards J, Livermore DM, Little P, Charlett A, Freeman E, et al. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *The Journal of antimicrobial chemotherapy*. 2006;58(5):1000-8.
25. Noskin GA, Zembower T, Chmielewski J, Tang P, La Rosa M, Peterson LR. Disappearance of the 'uncomplicated' urinary tract infection - The impact of emerging resistance. *Clinical Drug Investigation*. 2001;21:13-20.
26. Raz R, Chazan B, Kennes Y, Colodner R, Rottensterich E, Dan M, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2002;34(9):1165-9.
27. Soraas A, Sundsfjord A, Jorgensen SB, Liestol K, Jenum PA. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing *Escherichia coli*. *PloS one*. 2014;9(1):e85889.
28. Vallano A, Rodriguez D, Barcelo ME, Lopez A, Cano A, Vinado B, et al. [Antimicrobial susceptibility of uropathogens and outcome following antibiotic treatment for urinary tract infections in primary health care]. *Enfermedades infecciosas y microbiologia clinica*. 2006;24(7):418-25.
29. van Merode T, Nys S, Raets I, Stobberingh E. Acute uncomplicated lower urinary tract infections in general practice: clinical and microbiological cure rates after three- versus five-day treatment with trimethoprim. *The European journal of general practice*. 2005;11(2):55-8.
30. Cao B, Zhao CJ, Yin YD, Zhao F, Song SF, Bai L, et al. High prevalence of macrolide resistance in *Mycoplasma pneumoniae* isolates from adult and adolescent patients with respiratory tract infection in China. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2010;51(2):189-94.
31. Hagberg L, Carbon C, van Rensburg DJ, Fogarty C, Dunbar L, Pullman J. Telithromycin in the treatment of community-acquired pneumonia: a pooled analysis. *Respiratory medicine*. 2003;97(6):625-33.
32. Kawai Y, Miyashita N, Yamaguchi T, Saitoh A, Kondoh E, Fujimoto H, et al. Clinical efficacy of macrolide antibiotics against genetically determined macrolide-resistant *Mycoplasma pneumoniae* pneumonia in paediatric patients. *Respirology (Carlton, Vic)*. 2012;17(2):354-62.
33. O'Doherty B, Dutchman DA, Pettit R, Maroli A. Randomized, double-blind, comparative study of grepafloxacin and amoxycillin in the treatment of patients with community-acquired pneumonia. *The Journal of antimicrobial chemotherapy*. 1997;40 Suppl A:73-81.
34. van Rensburg DJ, Fogarty C, Kohno S, Dunbar L, Rangaraju M, Nusrat R. Efficacy of telithromycin in community-acquired pneumonia caused by pneumococci with reduced susceptibility to penicillin and/or erythromycin. *Chemotherapy*. 2005;51(4):186-92.
35. Yanagihara K, Otsu Y, Ohno H, Higashiyama Y, Miyazaki Y, Hirakata Y, et al. Clinical characteristics of pneumonia caused by penicillin resistant and sensitive *Streptococcus pneumoniae* in Japan. *Internal medicine (Tokyo, Japan)*. 2004;43(11):1029-33.

36. Zhanel GG, Wolter KD, Calciu C, Hogan P, Low DE, Weiss K, et al. Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant *Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data. *The Journal of antimicrobial chemotherapy*. 2014;69(10):2835-40.
37. Barry B, Gehanno P, Blumen M, Boucot I. Clinical outcome of acute otitis media caused by pneumococci with decreased susceptibility to penicillin. *Scandinavian journal of infectious diseases*. 1994;26(4):446-52.
38. Dagan R, Abramson O, Leibovitz E, Lang R, Goshen S, Greenberg D, et al. Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin. *The Pediatric infectious disease journal*. 1996;15(11):980-5.
39. Hoberman A, Paradise JL, Block S, Burch DJ, Jacobs MR, Balanescu MI. Efficacy of amoxicillin/clavulanate for acute otitis media: relation to *Streptococcus pneumoniae* susceptibility. *The Pediatric infectious disease journal*. 1996;15(10):955-62.
40. Hoberman A, Dagan R, Leibovitz E, Rosenblut A, Johnson CE, Huff A, et al. Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. *The Pediatric infectious disease journal*. 2005;24(6):525-32.
41. Quinn J, Ruoff GE, Ziter PS. Efficacy and tolerability of 5-day, once-daily telithromycin compared with 10-day, twice-daily clarithromycin for the treatment of group A beta-hemolytic streptococcal tonsillitis/pharyngitis: a multicenter, randomized, double-blind, parallel-group study. *Clinical therapeutics*. 2003;25(2):422-43.
42. Seppala H, Nissinen A, Jarvinen H, Huovinen S, Henriksson T, Herva E, et al. Resistance to erythromycin in group A streptococci. *The New England journal of medicine*. 1992;326(5):292-7.
43. Buchanan P, Roos K, Tellier G, Rangaraju M, Leroy B. Bacteriological efficacy of 5-day therapy with telithromycin in acute maxillary sinusitis. *International journal of antimicrobial agents*. 2005;25(3):237-46.
44. Dagan R, Bar-David Y. Double-blind study comparing erythromycin and mupirocin for treatment of impetigo in children: implications of a high prevalence of erythromycin-resistant *Staphylococcus aureus* strains. *Antimicrobial agents and chemotherapy*. 1992;36(2):287-90.
45. Giordano PA, Elston D, Akinlade BK, Weber K, Notario GF, Busman TA, et al. Cefdinir vs. cephalexin for mild to moderate uncomplicated skin and skin structure infections in adolescents and adults. *Current medical research and opinion*. 2006;22(12):2419-28.
46. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC infectious diseases*. 2014;14:13.
47. Coenen S, Goossens H. Antibiotic treatment failure in primary care. *BMJ (Clinical research ed)*. 2014;349:g5970.
48. Giesen LG, Cousins G, Dimitrov BD, van de Laar FA, Fahey T. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. *BMC family practice*. 2010;11:78.
49. Falagas ME, Kotsantis IK, Vouloumanou EK, Rafailidis PI. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. *The Journal of infection*. 2009;58(2):91-102.

Chapter 5 The relationship between antibiotic exposure and antibiotic “response failure” in children presenting with acute respiratory tract infections in primary care: an observational cohort study

5.1 Introduction

5.1.1 Background and rationale

Chapter 4 demonstrated the need to develop a better understanding of the relationship between antibiotic prescribing and development of clinically significant antibiotic resistance in the community. However, there are inherent problems identifying the likely pathogen for common infections in primary care because data on laboratory confirmed antibiotic-resistant infections are not routinely collected for common infections presenting in the community.(1) This is compounded by the fact that most infections managed in primary care are self-limiting and more viral than bacterial, which makes assessing the benefit from antibiotics difficult.(1) A recent systematic review highlighted a significant gap in the evidence for using clinical presentation to make a microbiological diagnosis for children presenting with respiratory tract infections, and concluded that there is insufficient evidence to recommend that clinicians perform routine microbial point-of-care tests for respiratory tract infections.(2) The main reason for this is that clinical symptoms and signs are unreliable to guide microbial point-of-care testing and improve targeting of antibiotics in children with upper respiratory tract infections.

For parents, the uncertainty as to whether their child’s infection is viral or bacterial is of less concern because there is often no meaningful trade-off: they are aware that the antibiotic would not work if their child’s infection was viral, but they believe that antibiotics would not do any harm; on the other hand, the antibiotic would be effective if the infection turned out to be bacterial. Therefore to maximise the chances of influencing behaviour, the consequences of unnecessary antibiotic use should have direct relevance and tangible outcomes for clinicians, patients and families in the community.

This chapter will explore the relationship between antibiotic exposure in children and subsequent acute respiratory tract infections (RTIs) that fail to respond to antibiotic treatment (“response failures”) in primary care.

5.1.2 Antibiotic exposure in childhood and its consequences

The highest rate of antibiotic prescribing occurs in children under 5 years old.(3-5). This ranges between one in six children receiving at least one oral antibiotic prescription per year based on a large Dutch cohort where national antibiotic prescribing is very low (3), to around 57% of all acute RTIs in the USA representing an estimated 11.4 million potentially preventable antibiotic prescriptions annually.(4) Many children will have had multiple antibiotic prescriptions within their early childhood. In a prospective cohort study (ALSPAC study) of over 13,000 pre-school children living in south-west England, 97% of children consulted primary care at least once over a 57 month period.(6) This is supported by studies in Melbourne Australia, where preschool children had 3.8 to 5 infections per person per year (7), and in New Zealand where each child had received a median of eight antibiotic courses [IQR 4-13] by the age of 5 years old.(8)

These figures are surprising because most of these infections are viral, self-limiting and do not benefit from antibiotic treatment.(9) This is at odds with current antibiotic prescribing guidance for self-limiting respiratory tract infections (RTI) in children (NICE guidelines 2008).(10) One reason may be that clinicians prescribe antibiotics when they felt pressured by parents or by others to do so (e.g. employers, day care) or misread parents’ expectations.(11, 12)

Exposure to antibiotics is likely to have important clinically relevant implications. Previous research of an all-age UK population showed that more than 1 in 10 patients prescribed antibiotics for common infections in the community experience a subsequent antibiotic ‘treatment failure’, mostly in the form of re-consultation and receipt of a different antibiotic prescription within 30 days of their initial prescription.(13) The presence of an antibiotic-resistant infection is one possible explanation for antibiotic “treatment failure”. The same authors also reported a treatment

failure rate of 9·2% in adolescents aged 12 to 17 years old with four common infections presenting in primary care (upper respiratory tract infections, lower respiratory tract infections, skin/soft tissue infections and acute otitis media) with the highest treatment failure rates for lower respiratory tract infections between 2000 and 2012.(14) A large study in the USA examining “antibiotic failure rates” in children with acute otitis media found that 10·1% were prescribed an additional antibiotic between 2 and 18 days over the 12 year study period. The latter study defined antibiotic failure as children who received a second prescription for an oral antibiotic, or were given injectable or intravenous antibiotics of a different class between 2 and 18 days after the first prescription. Children under 2 years old had the highest levels of antibiotic “treatment failure” (15-18%).(15)

There is robust evidence for an association between antibiotic use and the prevalence of resistant bacteria.(16, 17) More recently however, we are beginning to understand how antibiotic use may disrupt the protective gut and lung microbiomes and potentially predispose young children to increased susceptibility to certain bacterial and opportunistic pathogens with adverse health outcomes such as higher rates of respiratory tract infection (18), and subsequent RTIs which may not respond to antibiotics.(19, 20)

5.1.3 Concept of “failure to respond” to antibiotics in primary care

There is no consensus on the definition of antibiotic “treatment failure”.(21) Its definition is dynamic, malleable to a particular clinical context and has been described as a measure of the effectiveness of treatment e.g. length of hospital stay, higher mortality and greater healthcare costs in hospitals. In community studies, antibiotic “treatment failure” has been adapted and defined as any additional antibiotic prescriptions or hospitalisations for infections between 14 and 30 days after initial therapy (13, 22-24), referral to a hospital specialist (13, 25), recurrent or worsening infection or specific infective complications (26), and/or record of an emergency department visit.(13)

In primary care, the study by Currie et al. defines antibiotic “treatment failure” events within a 30 day window in the general population using CPRD data (13), as the earliest occurrence of:

- i. prescription of a subsequent antibiotic within 30 days of the initial antibiotic being prescribed,
- ii. GP record of hospital admission with an infection-related diagnostic code within 30 days of antibiotic initiation,
- iii. GP record of death with an infection-related diagnostic code within 30 days of antibiotic initiation,
- iv. GP record of referral to an infection-related specialist service within 30 days of antibiotic initiation, or
- v. GP record of an emergency department visit within three days of antibiotic initiation.

However, I have reconceptualised and adapted this definition as the term “clinical response failure” for three reasons. Firstly, “treatment failure” may occur for reasons other than failure of the antibiotic to treat a given infection. In other words, most children with respiratory tract infections do not respond to/benefit from antibiotics in the first place e.g. for a self-limiting (viral) RTI. Thus the antibiotics prescribed under these circumstances are not strictly speaking a “treatment”. Secondly, with reference to preschool children, the follow-up period for a subsequent antibiotic has been shortened (from 30 to 14 days) because hospital admission or complications of an infection are more likely to occur within a shorter period (27, 28), and young children can have more than one unique infectious episode in a 30 day period especially because day care attendance is common in this age group.(29, 30) Lastly, according to the British National Formulary for Children (BNFC, Chapter 5.1), the recommended oral antibiotic course typically lasts between 7-10 days for most common infections in children (31), and thus antibiotic “response failure” is judged to have occurred if infection symptoms have not improved following the completion of the antibiotic course. In the absence of routine microbiological sampling for respiratory tract infections in primary care, the term “response failure” gives a pragmatic,

clinically relevant outcome measure, irrespective of the mechanism by which it occurred, which can be extracted from routinely collected primary care data.

In order to better characterise and understand the epidemiology and impact of unnecessary antibiotic use over time in a primary care setting, this chapter will retrospectively analyse a large primary care database of routinely collected data to explore the potential impact of unnecessary antibiotic prescribing in children with RTIs in the community.

5.1.4 Aim and Objectives

The overall aim of this chapter is to examine the implications of antibiotic use in children in the community by exploring whether preschool children exposed to more antibiotics were more likely to get subsequent respiratory tract infections that do not respond to antibiotic treatment (antibiotic “response failures”).

The primary objective is to examine the relationship between the number of antibiotic prescriptions prescribed to preschool children for acute RTIs in the preceding year, and subsequent “response failure” in primary care.

The secondary objectives are:

- To determine the baseline consultation rate for acute RTI in preschool children i.e. the number of RTI consultations per 100,000 person-years of observation;
- To determine the proportion of acute RTI consultations that are associated with an antibiotic prescription in preschool children;
- To examine the relationship between the number of antibiotic prescriptions and antibiotic “response failures” in preschool children with upper versus lower RTIs.

5.2 Methods

5.2.1 Protocol

The protocol was submitted to the Independent Scientific Advisory Committee (ISAC) and approved 14 October 2016 (ISAC Protocol 16_162R).

5.2.2 The Clinical Practice Research Datalink (CPRD)

The CPRD is a UK national database of electronic medical records from 674 GP practices across England, Wales and Scotland.(32) This electronic database provides a comprehensive data source of anonymised longitudinal data from primary care, from around 5 million active patients (6.9% of the UK population) and is representative of the UK population (www.cprd.com).

The database includes records of all prescriptions issued, clinical diagnoses, referrals to secondary care, hospitalisations, and investigation results during consultations in primary care. Prescriptions are computer generated and are automatically incorporated into the patient medical record. The data have been extensively validated for pharmaco-epidemiological, clinical and health service usage research.(33-35)

This database study is an observational cohort study using routinely collected data from the CPRD. Data from 100,000 eligible children prescribed an antibiotic for acute RTIs from GP practices across the UK registered with the CPRD were sought. I considered a matched case control study design as we hypothesised that most acute RTIs are time-related (usually seasonal) i.e. when one child gets an acute RTI, many other children do so at similar times. A case control design would potentially be more efficient as it would involve a smaller data cut and the potential to match for other factors which may affect the likelihood of response failure. Matching would also attempt to correlate cases and controls according to similar pathogenic organisms recognising that different infections circulate at different times of the year.

However, the main motivation for considering a cohort design was that preschool children were likely to experience multiple RTI episodes within the 7-year study period. An “open” cohort design would allow evaluation of multiple presentations where antibiotics are prescribed in children presenting over the study period.(6-8)

5.2.3 Study population

Inclusion criteria

Children aged 12-60 months inclusive, prescribed an antibiotic for an acute RTI (upper-, lower RTI or otitis media) from January 2009 to September 2016 were included. This study period was chosen to allow sufficient opportunity for implementation of the NICE guidelines (July 2008) for prescribing of antibiotics for self-limiting RTIs (NICE guidance 2008).

Acute RTI were defined by one or more CPRD diagnostic codes (*Read* codes) relating to acute upper RTIs (e.g. rhinosinusitis) and lower RTIs (e.g. pneumonia, bronchitis), and otitis media (Appendix 13).

To calculate the baseline consultation rate for RTI, all children in the CPRD who presented to general practice for acute RTI (upper-, lower RTIs, AOM) during the study period were listed whether or not an antibiotic was prescribed. Secondly, all RTI consultations associated with an antibiotic prescription were identified, regardless of whether or not the outcome (“response failure”) subsequently occurred.

Antibiotic prescription included oral therapy with primarily antibacterial activity listed in the British National Formulary (BNF) for Children (Chapter 5.1) licensed for acute RTIs in young children, and defined by means of CPRD *product codes* listed in Appendix 14. Drugs with primarily antiviral or antifungal activity and drugs for non-acute RTI (e.g. tuberculosis) were excluded.

Those children issued antibiotic prescriptions at the index consultation where the *Read* code was missing, not relevant (not RTI-related) or had inadequate follow-up period, were excluded from the analysis. All children had to be registered in the CPRD database for at least 14 days after index consultation to allow the outcome to occur.

Exclusion criteria

Highly specific patient groups in whom specialised antibiotic regimens are recommended for chronic respiratory diseases (e.g. cystic fibrosis, tuberculosis) were excluded.

5.2.4 Sample size calculation

A recent CPRD study reported that 823,143, 614,701, and 206,413 patients were prescribed antibiotics for upper RTIs, lower RTIs or acute otitis media (AOM) respectively between 2008 and 2012. The study examined the incidence of antibiotic “treatment failure” events in the general population, in the form of re-consultation and receipt of a different antibiotic prescription within 30 days of their initial prescription.⁽¹³⁾ They found that 12·6%, 21·0%, 14·5% of patients respectively were classified as having antibiotic “treatment failures”. This study made no distinction between adults or children.

Based on 2011 Census data (Office for National Statistics, 2011 Census), which report that 6·2% of the UK population comprised of children aged less than 5 years old, and a conservative “response failure” rate estimate of 12% (see above), I estimated that, for example, with upper RTI, there will be 51,035 children under the age of 5 (and registered at general practices contributing data to CPRD) and 6,124 antibiotic “response failures”; Similarly, I estimated there will be 38,111 children and 4,573 antibiotic “response failures” with lower RTI, and 12,798 children, 1,535 antibiotic “response failures” with AOM.

A preliminary CPRD search was conducted to verify these numbers in September 2015. For the purposes of this study, there were 536,073 children, aged between 12 to 60 months, who had any record of RTI from 2009 to the most recent data cut. Assuming a conservative antibiotic

prescription rate of 20%, and again applying a conservative “response failure” rate estimate of 12%, the estimated number of children with acute RTI (upper, lower, AOM) and “response failure” is 12,866 antibiotic “response failures.

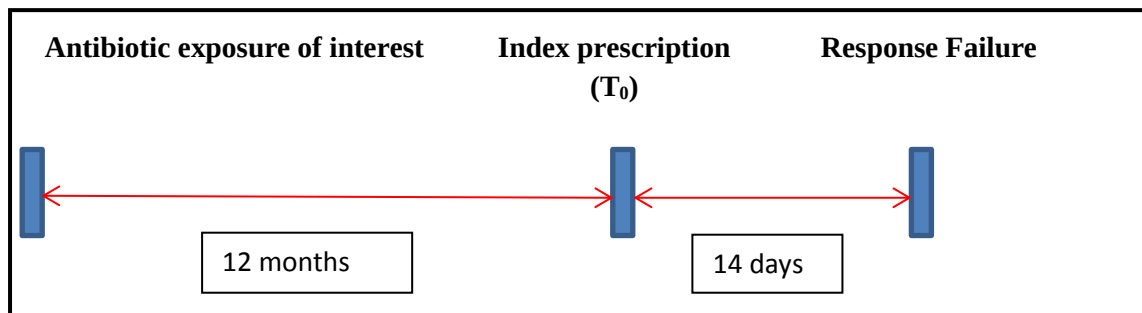
Based on the above, we estimated that there would be around 100,000 (20% of around 500,000) eligible children who will be prescribed an antibiotic for a RTI.

I consulted a senior statistician for advice in calculating the sample size based on these simple calculations above from published studies. We first used Stata 14.1 to calculate power, based on a sample size of 100,000, for a simple analysis of event rates in two groups. For an overall event rate (“response failure”) of 12%, an odds ratio (OR) of 0.94 would represent event rates 11.7% vs. 12.3%, for which two groups of 50,000 give 83% power. For the same overall event rate, an OR of 0.91, representing event rates 11.5% vs. 12.5%, gives 99.8% power. This calculation based on two groups is conservative, because the proposed analysis set out to examine antibiotic exposure as a continuous variable. Greater statistical power will arise because many children will contribute multiple observations as part of the secondary analysis (multi-level modelling).

5.2.5 Data management

Antibiotic exposure was measured as the number of antibiotic prescriptions for “acute RTI” up to 12 months prior to the index prescription (T_0) (Fig. 1). The reason for choosing a 12 month interval is that resistant bacterial carriage can last up to a maximum of one year for respiratory and urinary tract infections in adults and children.(16) However, in symptomatic children with acute RTIs, who were prescribed amoxicillin, antibiotic resistance has a transient peak of around 2-4 weeks after antibiotic consumption.(36)

Figure 1 Antibiotic exposure is the number of antibiotic prescriptions for acute RTIs up to 12 months prior to the index prescription (T_0)



The index prescription (T_0) was defined as the antibiotic prescription for an acute RTI. The antibiotic prescription is the unit of analysis for the primary analysis. All antibiotic prescriptions associated with acute RTIs up to 12 months prior to the index prescription were counted.

Covariates for adjustment were (Appendix 15):

- age (years) at the time of index antibiotic prescription,
- sex,
- time of year (according to seasons: Dec-Feb = winter; Mar-May = spring; Jun-Aug = summer; Sept-Nov = autumn),
- RTI type (upper-, lower RTI, and otitis media),
- class of antibiotic (according to the BNFC classification),
- presence of one or more comorbidity,
- childhood vaccination status: diphtheria, tetanus, pertussis, polio and Hib (DTaP/IPV/Hib) and pneumococcal conjugate (PCV),
- social deprivation quintiles based on patient-linked deprivation index score (IMD),
- number of previous “response failure” episodes during the 12-month period before the index prescription, and
- number of consultations for acute RTIs during the 12 months before the index prescription (baseline consultation rate).

5.2.6 Outcome

The outcome was antibiotic “response failure”. As explained in 5.1.3, the definition of “response failure” was adapted from a recent study which examined the incidence of these events using CPRD data.(13)

“Response failure” was defined as the earliest occurrence of any of:

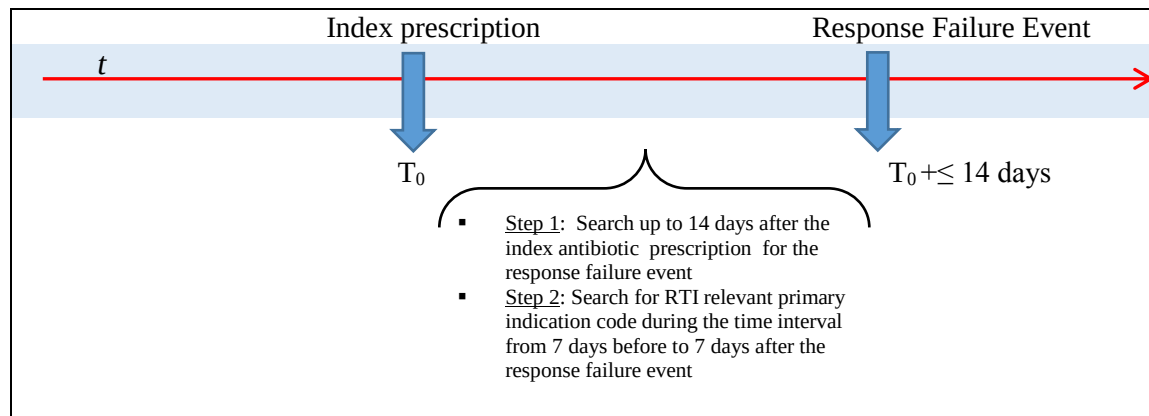
- i. prescription of a subsequent antibiotic within 14 days of the initial antibiotic being prescribed to that child,
- ii. GP record of hospital admission with an infection-related diagnostic code within 14 days of antibiotic initiation,
- iii. GP record of death with an infection-related diagnostic code within 14 days of antibiotic initiation,
- iv. GP record of referral to an infection-related specialist service within 14 days of antibiotic initiation, or
- v. GP record of an emergency department visit within three days of antibiotic initiation.

Referrals to a specialist service in secondary care were taken out of the “referrals file” within the CPRD. This file contains information about who the referral is made to, and is not linked to a CPRD diagnostic code. One of the CPRD data managers (Mrs Alice Fuller) helped match referrals to secondary care by index consultation dates and selected acute specialities relevant to acute infections with a RTI diagnostic code. Referrals for blood tests, microbiology (throat or ear swabs etc.) were excluded. Where it was not clear where the referral was being made to, referrals were based on probable acute RTI-related symptoms e.g. breathlessness.

For each index antibiotic prescription (T_0), “response failure” events were derived by searching forward 14 days from T_0 for the first indication of “response failure” as per the definition thereof. This is detailed in Fig 2. For those children who fulfilled one of the criteria of “response failure”,

any RTI relevant primary indication code (READ) was sought either side of the “response failure” event.

Figure 2 Derivation of “response failure”



t : time; RTI: respiratory tract infection; T_0 : index antibiotic prescription

Adapted from Currie et al. 2014(13)

5.2.7 Descriptive analysis

Data were summarised as numbers and percentages for categorical variables, and means and standard deviations for continuous variables where appropriate.

The aim was to analyse the number of antibiotic courses for acute RTIs in the preceding year (antibiotic exposure) as a continuous variable. However, if the distribution of antibiotic courses was skewed, antibiotic exposure would be recoded as a categorical variable. The overall proportion of acute RTI consultations that were associated with an antibiotic prescription was calculated as the number of RTI consultations where an antibiotic was prescribed divided by the number of all RTI consultations.

5.2.8 Statistical analysis

I performed two analyses using this study design: a multivariable logistic regression analysis on a random sample of children (primary analysis) and multivariable logistic regression using a three-level mixed effects model (secondary analysis).

(a) Primary analysis

The primary analysis included one random index antibiotic prescription for RTI per child during the study period 2009-2016. The selection of the random sample of episodes within children was derived using the STATA *set seed* randomisation command. One of the CPRD data managers (Mrs Alice Fuller) assisted me with the randomisation and preparation of the dataset.

To examine the association between the number of antibiotic courses for acute RTIs in the preceding 12 months and “response failure”, I calculated unadjusted and adjusted odds ratios with 95% confidence intervals in relation to the study outcome using multivariable logistic regression.

(b) Secondary analysis

To account for multiple individual RTI episodes presenting in each child nested within each practice, I carried out multivariable logistic regression using a three-level mixed effects model to examine whether (i) GP practice-level, (ii) child-level factors and (iii) antibiotic prescriptions were associated with “response failure” adjusting for covariates outlined above in 5.2.5.

(c) Sensitivity analyses

To assess the robustness of the primary analysis, sensitivity analyses were performed, which excluded data from:

- i. index antibiotic prescribing episodes which were preceded by one or more antibiotic prescriptions within the last 14 days. These episodes may be response failures rather than index prescriptions based on our study definition;
- ii. index antibiotic prescribing episodes which were preceded by one or more antibiotic prescriptions during the 8-week period before the index prescription. Individuals with self-limiting respiratory tract infections may continue to experience symptoms such as persistent cough for up to eight weeks.(37, 38) Antibiotic prescriptions issued during the 8-week period before the index prescription may therefore represent

unnecessary antibiotic prescribing during the natural course of the illness rather than failure of the illness to respond to antibiotics; and

- iii. children who were 12 months of age at the time of index prescription since these children would only have data from the time the child was registered at the GP surgery and may not have 12 months data in the CPRD.

An additional sensitivity analysis was also performed whereby the response failure outcomes were only defined as criteria ii-v of the outcome definition thereby minimising the behavioural aspects of parental consultation and antibiotic prescribing.

(d) Subgroup analysis

Subgroup analysis was performed by RTI type (upper RTI vs lower RTIs vs otitis media).

5.3 Results

During the study period, there were 252,572 preschool children from 1,546,364 consultations who presented to general practice for acute RTIs (upper-, lower RTIs, AOM) regardless of whether an antibiotic course was prescribed. The proportion of children prescribed an antibiotic for acute RTI was 45% (114,329/252,572) during the study period. Overall, during the study period, the average number of consultations for acute RTI per child was six.

5.3.1 Primary Analysis

Baseline characteristics

In the random sample, there were 114,329 children with an antibiotic prescription for RTI during the study period. Baseline characteristics of this cohort are shown in Table 1. The median baseline consultation rate for RTI was 4 (IQR 2 to 7) in the previous year. The median age of children was 2.39 years (IQR 1.39 to 3.66). Around 6% (n=6,625; 5.79%) had a listed comorbidity. Asthma

(n=3,134; 47·31%) was the most common comorbidity. A third of children had a history of premature birth (n=2,201; 33·22%).

Just over a third of children (41,830; 36·59%) presented in the winter months. Almost two-thirds of antibiotics associated with a RTI code were prescribed for LRTI (n=68,634; 60·03%), followed by AOM (n=28,604; 25·02%) and URTI (n=16,048; 14·04%). A small proportion of children had both LRTI and URTI codes (n=622; 0·58%) on the same consultation day. Less than 3% of children had a history of one or two previous response failures during the 12 months prior to the index RTI consultation.

Table 1 Demographic and clinical characteristics of study population. Random sample of preschool children prescribed antibiotics for an acute RTI in the CPRD 2 January 2009 to 23 September 2016 (N=114,329)

Characteristic	Number (%) or median (interquartile range)
Age in years (median, IQR)	2.39 yr (IQR 1.39 to 3.66)
Gender (female)	54,379 (47·56%)
Season ^a	
Winter	41,830 (36·59%)
Spring	30,110 (26·34%)
Summer	15,108 (13·21%)
Autumn	27,281 (23·86%)
RTI type ^b	
URTI	16,048 (14·04%)
LRTI	68,634 (60·03%)
AOM	28,604 (25·02%)
URTI & LRTI	662 (0·58%)
Other mix	381 (0·33%)
Comorbidity	6,625 (5·79%)
Antibiotic class	
Cephalosporin	847 (0·74%)
Macrolides	11,571 (10·12%)
Broad-spectrum penicillin (amoxicillin; co-amoxiclav)	87,723 (76·73%)
Penicillinase-resistant (flucloxacillin)	275 (0·24%)
Penicillin V	13,673 (11·96%)
Quinolones	7 (0·01%)
Trimethoprim-cotrimoxazole	233 (0·20%)
Vaccination status at index date (complete) ^c	43,401 (37·96%)
Vaccination status at end of study period (complete) ^c	106,803 (93·42%)
Social deprivation quintiles ^d	
1 (least deprived)	25,125 (21·99%)
2	23,021 (20·15%)
3	20,935 (18·32%)

4	23,186	(20·29%)
5 (most deprived)	21,994	(19·25%)
Not linked to IMD	68	(0·06%)
Previous response failures ^e in last 12 months		
None	111,281	(97·33%)
1	3,011	(2·63%)
2	37	(0·03%)
Previous RTI consultations in last 12 months (median, IQR)		
4 (IQR 2-7)		
Number of children with an RTI-associated antibiotic prescription during the 12 months before the index consultation		
None	95,383	(83·43%)
1	14,929	(13·06%)
>2	4,017	(3·51%)

^a Seasons: Winter (Dec-Feb); Spring (Mar-May); Summer (Jun-Aug); Autumn (Sept-Nov)

^b URTI: acute sinusitis, sore throat, laryngitis, coughs etc.; LRTI: pneumonia, bronchitis etc.; AOM: acute otitis media; URTI & LRTI: two separate RTI READ codes for antibiotic prescribing event.

^c Complete set of specific vaccinations appropriate for age

^d Index of Multiple Deprivation (IMD) quintile based on patient-linked IMD scores 2010

^e Response failure is defined as the earliest occurrence of any of:

- prescription of a subsequent antibiotic within 14 days of the initial antibiotic being prescribed to that child;
- GP record of admission with an infection-related diagnostic code[†]
- GP record of death with an infection-related diagnostic code[†]
- GP record of referral to an infection-related specialist service[†] ([†]all within 14 days of antibiotic initiation); or
- GP record of an emergency department visit within three days of antibiotic initiation.

Antibiotic exposure

The distribution of antibiotic exposure was positively skewed. There were 18, 946 (16·57%) children who received at least one antibiotic prescription associated with a RTI code during the 12 month period before the index RTI consultation. 14,929 (13·06 %) children had one, and 4,017 (3·51%) children had two or more RTI-associated antibiotic prescriptions in the 12 months prior to the index prescription. The most common antibiotic prescribed at the index consultation was a broad-spectrum penicillin (n=87,723; 76·73%).

Response Failure

In the primary analysis, we observed 1,337 response failures, of which 724 (52·58%) were referrals to an infection-related specialist service in secondary care, 306 (22·22%) were subsequent antibiotic prescriptions, 243 (17·65%) were emergency department visits within three days, 103 (7·48%) were hospital admissions, and one death (Table 2). Around half of referrals

were to Paediatric and Ear Nose & Throat specialities. Just under a quarter of referrals (23%; 167/724) were based on symptoms related to probable acute RTI.

Table 2 Antibiotic exposure in the 12 months prior to index consultation and response failure criteria. Values are numbers of children.

Antibiotic exposure	Response failure					
	Referral	Second prescription	Emergency department visit	Hospital admission	Death	Total
None	494	268	209	78	1	1,050
1	153	32	28	17	0	230
≥ 2	77	6	6	8	0	97
antibiotic courses						
Total	724 ^a	306 ^b	243 ^c	103 ^d	1 ^e	1,377

- a: Days to referral (median, IQR) = 2 days (0-7)
- b: Days to second prescription (median, IQR) = 10 days (7-13)
- c: Days to emergency visit (median, IQR) = 2 days (1-7)
- d: Days to hospital admission (median, IQR) = 2 days (1-9)
- e: Death occurred at day 5

Odds of response failure

Children who received two or more antibiotic courses for “acute RTI” in the preceding year had greater likelihood of “response failure” even after adjusting for covariates (unadjusted odds ratio (OR) 2.22 [1.80 to 2.74], $p < 0.001$; adjusted OR 1.32 [95% CI 1.04-1.66], $p = 0.02$, $n = 97$; Table 3). Greater odds of response failure were also observed in children who had one antibiotic course during the previous year, but this result was no longer statistically significant after adjustment (unadjusted OR 1.41 [1.22 to 1.62], $p < 0.001$; adjusted OR 1.03 [95% CI 0.88-1.21], $p = 0.67$). In the multivariable model, the following covariates for adjustment were statistically significant: age; gender; comorbidity; number of response failures in previous year; number of acute RTI consultations in previous year; and vaccination status at index consultation.

Table 3 Primary analysis: multivariable analysis of the association between RTI-associated antibiotic exposure in the previous year and subsequent “response failure” for acute RTI (n=1,377 response failures)

Variable	Adjusted Odds Ratio [95% CI]	P value
Number of RTI antibiotic prescriptions in previous year (no. of children)		
None (n=1,050)	1 [Reference]	
1 antibiotic (n=230)	1.03 [0.88-1.21]	0.67
≥2 antibiotics (n=97)	1.32 [1.04-1.66]	0.02
Age at index consultation (years)	0.95 [0.90 to 0.99]	0.018
Gender		
Male	1 [Reference]	
Female	0.85 [0.76 to 0.95]	0.003
Season ^a		
Winter	1 [Reference]	
Spring	1.09 [0.96 to 1.26]	0.18
Summer	1.22 [1.03 to 1.43]	0.02
Autumn	1.00 [0.87 to 1.16]	0.99
RTI type ^b		
URTI	1 [Reference]	
LRTI	0.88 [0.75 to 1.04]	0.13
AOM	1.05 [0.88 to 1.25]	0.60
URTI and LRTI	2.37 [1.48 to 3.79]	<0.001
Other mix	0.84 [0.31 to 2.27]	0.73
Comorbidity		
None	1 [Reference]	
Present	1.20 [0.98 to 1.48]	0.08
Antibiotic drug class		
Cephalosporin	1 [Reference]	
Macrolides	0.77 [0.50 to 1.19]	0.25
Broad spectrum penicillin (amoxicillin, co-amoxiclav)	0.47 [0.30 to 0.71]	0.001
Penicillinase-resistant (flucloxacillin)	0.46 [0.14 to 1.54]	0.21
Pen V (phenoxymethylpenicillin)	0.60 [0.39 to 0.94]	0.03
Quinolones	0 (empty)	
Trimethoprim-cotrimoxazole	1.01 [0.41 to 2.53]	0.98
Number of response failures in previous year		
None	1 [Reference]	
1	2.08 [1.67 to 2.58]	<0.001
2	3.93 [1.18 to 13.12]	0.03
Number of acute RTI consultations in previous year	1.03 [1.02 to 1.05]	<0.001
Social Deprivation		
1 (least deprived)	1 [Reference]	
2	0.96 [0.81 to 1.13]	0.61
3	1.08 [0.92 to 1.28]	0.34
4	1.12 [0.95 to 1.32]	0.17
5 (most deprived)	0.99 [0.84 to 1.18]	0.96
Vaccination status at index consultation		
Incomplete or none	1 [Reference]	

Complete	1·41 [1·26 to 1·59]	<0·001
----------	---------------------	--------

^a Seasons: Winter (Dec-Feb); Spring (Mar-May); Summer (Jun-Aug); Autumn (Sept-Nov)

^b URTI: acute sinusitis, sore throat, laryngitis, coughs etc.; LRTI: pneumonia, bronchitis etc.; AOM: acute otitis media; URTI & LRTI: two separate RTI READ codes for antibiotic prescribing event.

5.3.2 Secondary analysis

Incorporating multiple RTI episodes in each child, there were 190,290 acute RTI episodes in 114,329 children from 380 GP practices during the study period. Baseline characteristics of this cohort are shown in Table 4.

Table 4 Demographic and clinical characteristics of study population. Multiple RTI episodes in preschool children prescribed antibiotics for an acute RTI in the CPRD, 2 January 2009 to 23 September 2016 (N= 190,290 RTI episodes in 114,329 preschool children)

Characteristic	Number (%) or median (interquartile range)
Number of GP practices	380
Age in years (median, IQR)	2.73 yr (IQR 1.66 to 3.82)
Gender (female)	54,379 (47·56%)
Season	
Winter	68,154 (35·82%)
Spring	50,628 (26·61%)
Summer	26,029 (13·68%)
Autumn	45,479 (23·90%)
RTI type ^a	
URT	26,265 (13·80%)
LRT	115,772 (60·84%)
AOM	47,210 (24·81%)
URT & LRT	662 (0·35%)
Other mix	381 (0·20%)
Comorbidity	13,257 (6·97%)
Antibiotic class	
Cephalosporin	1,702 (0·89%)
Macrolides	22,727 (11·94%)
Broad-spectrum penicillin (amoxicillin; co-amoxiclav)	141,196 (74·20%)
Flucloxacillin	440 (0·23%)
Penicillin V	23,760 (12·49%)
Quinolones	30 (0·02%)
Trimethoprim-cotrimoxazole	435 (0·23%)
Vaccination status at index date (complete)	117,142 (61·56%)
Social deprivation quintiles ^b	
1 (least deprived)	41,644 (21·90%)
2	38,462 (20·22%)
3	34,995 (18·40%)

4	38,713 (20·36%)
5 (most deprived)	36,369 (19·12%)
Not linked to IMD	107 (0·06%)
Previous response failures ^c in last 12 months	
None	187,242 (99·40%)
1	3,011 (1·58%)
2	37 (0·02%)
Previous RTI consultations in last 12 months (median, IQR)	1 (IQR 0-5)
Number of RTI episodes with an RTI-associated antibiotic prescription during the 12 months before the index consultation	
None	126,869 (66·67%)
1	43,699 (22·96%)
≥2	19,722 (10·36%)

^a URTI: acute sinusitis, sore throat, laryngitis, coughs etc ; LRTI: pneumonia, bronchitis etc; AOM: acute otitis media; URTI & LRTI: two separate RTI READ codes for antibiotic prescribing event.

^b Index of Multiple Deprivation (IMD) quintile based on patient-linked IMD scores 2010

^c Response failure is defined as the earliest occurrence of any of:

- prescription of a subsequent antibiotic within 14 days of the initial antibiotic being prescribed to that child;
- GP record of admission with an infection-related diagnostic code[†]
- GP record of death with an infection-related diagnostic code[†]
- GP record of referral to an infection-related specialist service[†] (*all within 14 days of antibiotic initiation); or
- GP record of an emergency department visit within three days of antibiotic initiation.

Response failure

There were 3,709 response failures. The median number of response failures per practice was 8 IQR [4 to 14] during the study period. Subsequent antibiotic prescriptions (1,757, 47·37%) was now the top criterion for response failure. This was followed by referrals to an infection-related specialist service in secondary care (1,359, 36·64%); emergency department visits within three days (426, 11·49%); hospital admissions (166, 4·48%) and one death (Appendix 16).

Odds of response failure

When accounting for multiple individual RTI episodes presenting in each child nested within each general practice, the secondary analysis supported the findings from the primary analysis. Greater odds of response failure were observed in children who had one antibiotic course during the previous year (one antibiotic course: unadjusted odds ratio (OR) 1·62 [1·50 to 1·75], $p < 0.001$; adjusted OR 1·16 [95% CI 1·07-1·27], $p < 0.001$, $n = 1,029$). This likelihood of response failure was greater for children who had two or more antibiotic courses during the previous year: unadjusted

odds ratio (OR) 2.92 [2.68 to 3.17], $p < 0.001$; adjusted OR 1.92 [95% CI 1.75-2.10], $p < 0.001$, $n=820$; Table 5).

Table 5 Secondary analysis: three-level mixed effects model of the association between multiple RTI-associated antibiotic exposure in the previous year and subsequent “response failure” for acute RTI ($n=3,709$ response failures)

Variable	Adjusted Odds Ratio [95% CI]	P value
Number of RTI antibiotic prescriptions in previous year (no. of children)		
None ($n= 1,860$)	1 [Reference]	
1 antibiotic ($n= 1,029$)	1.16 [1.07-1.27]	<0.001
≥ 2 antibiotics ($n= 820$)	1.92 [1.75-2.10]	<0.001
Age at index consultation (years)	1.04 [1.01 to 1.07]	0.006
Gender		
Male	1 [Reference]	
Female	0.93 [0.88 to 0.99]	0.04
Season		
Winter	1 [Reference]	
Spring	1.05 [0.97 to 1.15]	0.21
Summer	0.98 [0.89 to 1.09]	0.75
Autumn	0.96 [0.87 to 1.04]	0.31
RTI type		
URTI	1 [Reference]	
LRTI	0.93 [0.84 to 1.03]	0.20
AOM	1.21 [1.09 to 1.36]	0.001
URTI and LRTI	2.12 [1.33 to 3.36]	0.002
Other	0.78 [0.29 to 2.11]	0.62
Comorbidity		
None	1 [Reference]	
Present	1.30 [1.16 to 1.45]	<0.001
Antibiotic drug class		
Cephalosporin	1 [Reference]	
Macrolides	0.93 [0.70 to 1.23]	0.62
Broad spectrum penicillin (amoxicillin, co-amoxiclav)	0.58 [0.44 to 0.76]	<0.001
Penicillinase-resistant (flucloxacillin)	0.74 [0.36 to 1.52]	0.41
Pen V (phenoxymethylpenicillin)	0.88 [0.67 to 1.17]	0.40
Quinolones	1.47 [0.34 to 6.40]	0.61
Trimethoprim-cotrimoxazole	0.88 [0.47 to 1.63]	0.68
Number of response failures in previous year		
None	1 [Reference]	
1	1.79 [1.44 to 2.21]	<0.001
2	4.74 [1.41 to 15.93]	0.01
Number of acute RTI consultations in previous year	0.98 [0.97 to 0.99]	<0.001
Social Deprivation		

1 (least deprived)	1 [Reference]	
2	1.06 [0.96 to 1.18]	0.27
3	1.07 [0.96 to 1.19]	0.24
4	1.09 [0.97 to 1.22]	0.13
5 (most deprived)	1.04 [0.92 to 1.16]	0.52
Vaccination status at index consultation		
Incomplete or none	1 [Reference]	
Complete	1.87 [1.71 to 2.05]	<0.001

5.3.3 Sensitivity analyses

When I excluded RTI-associated antibiotic prescribing episodes which were preceded by one or more antibiotic courses within the last 14 days (since these episodes may be response failures rather than index prescriptions based on our study definition), the association between ≥ 2 antibiotic courses and response failure was of borderline statistical significance: one antibiotic course: adjusted OR 1.00 [95% CI 0.85-1.18], $p=0.98$; two or more antibiotic courses: OR 1.28 [95% CI 1.01-1.61], $p=0.046$ (Appendix 17).

When excluding antibiotic prescribing episodes which were preceded by one or more antibiotic prescriptions during the 8-week period before the index prescription, a statistically significant association was not demonstrated between children receiving two or more course of antibiotics and “response failure”: two or more antibiotic courses: OR 1.13 [95% CI 0.86-1.47], $p=0.38$ (Appendix 17). However, children receiving one antibiotic course in the previous year were less likely to have “response failure”: one antibiotic course: adjusted OR 0.83 [95% CI 0.69-0.98], $p=0.03$.

Children who were 12 months of age at the time of index prescription may not have 12 months data in the CPRD. However, excluding these children (14,438 excluded; 12.62%) did not change the overall results: one antibiotic course: adjusted OR 1.03 [95% CI 0.87-1.22], $p=0.75$; two or more antibiotics courses: OR 1.29 [95% CI 1.01-1.64], $p=0.04$ (Appendix 18).

By excluding children where the first criterion of our study outcome was used (i.e. prescription of a subsequent antibiotic within 14 days of the initial antibiotic being prescribed to that child; $n=306$ excluded), I observed that the prescription of one antibiotic was associated with

significantly increased risk of response failure (adjusted OR 1.21 [95% CI 1.02-1.44], $p=0.03$), as was prescription of two or more antibiotics (OR 1.54 [95% CI 1.20-1.98], $p=0.001$ (Appendix 18).

5.3.4 Subgroup analysis

Children who received two or more antibiotic courses specifically with a lower RTI ($n=68,634$) in the preceding 12 months were more likely to have “response failure” (one antibiotic course: OR 1.13 [95% CI 0.92-1.39], $p=0.25$; two or more antibiotic courses: OR 1.60 [95% CI 1.19-2.16], $p=0.002$. A statistically significant association was not observed for the other four categories of acute RTI coded in the CPRD.

5.4 Discussion

5.4.1 Main findings

Preschool children who received two or more antibiotic courses in the previous year for acute RTI had greater likelihood of antibiotic “response failure” to treatment for subsequent acute RTIs compared to children that had received no previous antibiotics. In the primary analysis, referrals to a specialist service in secondary care accounted for around half of response failures. When accounting for multiple individual RTI episodes presenting in each child nested within each general practice, secondary analysis supported the findings from the primary analysis.

5.4.2 Strengths and Limitations

5.4.2.1. Strengths

In the absence of routine microbiological sampling for acute RTIs in primary care, the estimates for “response failure” give a pragmatic, clinically relevant outcome measure that patients and clinicians in the community can relate to.

A major strength of this study is the scale and quality of routinely collected primary care data to conduct this study limiting information bias. This cohort of preschool children is also broadly representative of preschool children across the UK, and therefore the results are likely to be generalisable to similar paediatric populations.

I have focussed on a subset of the population in the community where the highest rate of antibiotic prescribing occurs and where unnecessary antibiotic exposure disrupts the normally protective bacterial flora. Important clinical factors specific to young children with acute RTIs have been incorporated into the definition of antibiotic “response failure” e.g. a shortened follow-up period of 14 days, and adjusted for baseline consultation rate and previous response failures.

An important methodological strength is that the main findings are supported by the secondary analysis, where I have taken into account multiple RTI episodes in each child nested in GP practices over the study period.

5.4.2.2. Limitations

Available data were unable to explain whether the antibiotic prescription was redeemed or taken correctly, or whether an antibiotic course was prescribed appropriately. Likewise, the true aetiology of these acute RTIs is not known. Therefore evidence of antibiotic non-response may relate to sub-optimal diagnosis and inappropriate treatment rather than lack of effectiveness in the treatment of bacterial infections. Likewise, the definition of antibiotic response failure does not capture whether the failure was truly a clinical failure or a response to an adverse reaction to the index antibiotic prescription. Therefore, against a backdrop of unnecessary antibiotic use, these data cannot report the relative contribution of bacterial resistance or answer the question of causality or appropriateness of the antibiotic prescription.

I accept that those children frequently attending their GP might be more likely to have prior antibiotic exposure. However, it is unclear how an antibiotic prescription per se impacts upon subsequent consultation behaviour in primary care. For example, in one trial of adults and

children with acute RTI in the UK, patients receiving an antibiotic course were less likely to re-consult within a month (39), yet an earlier trial reported that prescribing antibiotics for sore throat increased the chances of re-consulting (38% versus 27%), with an additional effect from prior antibiotic prescribing.(41) My analysis however, took into account baseline consultation rate of children.

Most response failures were due to referral to a specialist service in secondary care, and children receiving two or more previous antibiotic courses (not just one previous course) had greater odds of response failure. This suggests that response failures in children may represent more complex situations than simply a greater parental belief or desire for antibiotics.

CPRD data does not allow reliable differentiation between immediate and delayed antibiotic prescriptions. However, based on recent survey data, delayed prescriptions in the UK is probably rarer than thought ranging between 4-14 %.(40, 41) This is supported by a prospective cohort study of over 8,000 UK children (TARGET study) who consulted for acute cough or RTI, where only 8% received a delayed antibiotic prescription, of which 42% consumed them on the day of receiving the script.(28, 42)

This analysis is limited to previous antibiotic prescriptions associated with acute RTIs in preschool children as opposed to any infection. Although similar antibiotic classes (e.g. amoxicillin) are used for urinary tract infections in children, in terms of antibiotic consumption, the proportion of young children seen in UK primary care with a urinary tract infection is only around 6% (43), compared to around 66% for acute RTIs.(44)

Although I adjusted for important covariates, it was not possible to account for confounding due to illness severity from routinely collected data, as data on clinical features relating to illness severity, including vital sign measurements, indicators of respiratory distress, and duration of illness, are not consistently coded during primary care consultations. The findings may be identifying children that are prone to infections (but without a relevant comorbidity) without identifying the association with number of antibiotic prescriptions. However, this research output

is useful to help define patient-level surveillance standards in the community to assess how much antibiotic prescribing is likely to be problematic in terms of increasing the likelihood of “response failure”.

5.4.3 Conclusion

Preschool children who received two or more antibiotic courses in the previous year for acute RTI had greater odds of antibiotic “response failure” to treatment for subsequent acute RTIs. These findings demonstrate that every day antibiotic prescribing decisions for young children in the community have unanticipated consequences. Clinicians and parents should consider previous antibiotic exposure when making decisions about whether further antibiotics are likely to be beneficial when children consult with acute RTIs. They should exercise particular caution in relation to prescribing decisions in children who have received two or more antibiotic prescriptions during the previous 12 months.

However, the underlying causes of children not responding to antibiotics are multifactorial and complex. A significant proportion of consultations (and re-consultations) will probably be associated with parents’ health seeking behaviour and how they view the benefits and risks of antibiotic treatment for their young child. Chapter 6 will now explore these issues and relate these to antibiotic resistance.

5.5 References

1. Bordado Skold M, Aabenhus R, Guassora AD, Makela M. Antibiotic treatment failure when consulting patients with respiratory tract infections in general practice. A qualitative study to explore Danish general practitioners' perspectives. *The European journal of general practice*. 2017;23(1):120-7.
2. Thornton HV, Blair PS, Lovering AM, Muir P, Hay AD. Clinical presentation and microbiological diagnosis in paediatric respiratory tract infection: a systematic review. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2015;65(631):e69-81.
3. de Bont EG, van Loo IH, Dukers-Muijters NH, Hoebe CJ, Bruggeman CA, Dinant GJ, et al. Oral and topical antibiotic prescriptions for children in general practice. *Archives of disease in childhood*. 2013;98(3):228-31.

4. Kronman MP, Zhou C, Mangione-Smith R. Bacterial prevalence and antimicrobial prescribing trends for acute respiratory tract infections. *Pediatrics*. 2014;134(4):e956-65.
5. Holstiege J, Schink T, Molokhia M, Mazzaglia G, Innocenti F, Oteri A, et al. Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study. *BMC Pediatrics*. 2014;14(1):174.
6. Hay AD, Heron J, Ness A. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. *Family practice*. 2005;22(4):367-74.
7. Leder K, Sinclair MI, Mitakakis TZ, Hellard ME, Forbes A. A community-based study of respiratory episodes in Melbourne, Australia. *Australian and New Zealand journal of public health*. 2003;27(4):399-404.
8. Hobbs MR, Grant CC, Ritchie SR, Chelimo C, Morton SMB, Berry S, et al. Antibiotic consumption by New Zealand children: exposure is near universal by the age of 5 years. *The Journal of antimicrobial chemotherapy*. 2017;72(6):1832-40.
9. Harnden A, Perera R, Brueggemann AB, Mayon-White R, Crook DW, Thomson A, et al. Respiratory infections for which general practitioners consider prescribing an antibiotic: a prospective study. *Archives of disease in childhood*. 2007;92(7):594-7.
10. National Institute for Health and Clinical Excellence. Respiratory Tract Infections - Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care. London: National Institute for Health and Clinical Excellence (UK); 2008.
11. Fletcher-Lartey S, Yee M, Gaarslev C, Khan R. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. *BMJ open*. 2016;6(10):e012244.
12. Lucas PJ, Cabral C, Hay AD, Horwood J. A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. *Scandinavian journal of primary health care*. 2015;33(1):11-20.
13. Currie CJ, Berni E, Jenkins-Jones S, Poole CD, Ouwens M, Driessen S, et al. Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. *BMJ (Clinical research ed)*. 2014;349:g5493.
14. Berni E, Scott LA, Jenkins-Jones S, De Voogd H, Rocha MS, Butler CC, et al. Non-Response to Antibiotic Treatment in Adolescents for Four Common Infections in UK Primary Care 1991-2012: A Retrospective, Longitudinal Study. *Antibiotics (Basel, Switzerland)*. 2016;5(3).
15. McGrath LJ, Becker-Dreps S, Pate V, Brookhart MA. Trends in antibiotic treatment of acute otitis media and treatment failure in children, 2000-2011. *PloS one*. 2013;8(12):e81210.
16. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2010;340:c2096.
17. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005;365(9459):579-87.
18. Biesbroek G, Tsvitshivadze E, Sanders EA, Montijn R, Veenhoven RH, Keijser BJ, et al. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. *American journal of respiratory and critical care medicine*. 2014;190(11):1283-92.
19. Johnson CL, Versalovic J. The human microbiome and its potential importance to pediatrics. *Pediatrics*. 2012;129(5):950-60.
20. Doan T, Arzika AM, Ray KJ, Cotter SY, Kim J, Maliki R, et al. Gut Microbial Diversity in Antibiotic-Naive Children After Systemic Antibiotic Exposure: A Randomized Controlled Trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2017;64(9):1147-53.
21. Sanchez Garcia M. Early antibiotic treatment failure. *International journal of antimicrobial agents*. 2009;34 Suppl 3:S14-9.

22. Hess G, Hill JW, Raut MK, Fisher AC, Mody S, Schein JR, et al. Comparative antibiotic failure rates in the treatment of community-acquired pneumonia: Results from a claims analysis. *Advances in therapy*. 2010;27(10):743-55.
23. Longo C, Bartlett G, Macgibbon B, Mayo N, Rosenberg E, Nadeau L, et al. The effect of obesity on antibiotic treatment failure: a historical cohort study. *Pharmacoepidemiology and drug safety*. 2013;22(9):970-6.
24. Soraas A, Sundsfjord A, Jorgensen SB, Liestol K, Jenum PA. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing *Escherichia coli*. *PloS one*. 2014;9(1):e85889.
25. Murray H, Stiell I, Wells G. Treatment failure in emergency department patients with cellulitis. *Cjem*. 2005;7(4):228-34.
26. Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2012;55(5):651-62.
27. Chonmaitree T, Trujillo R, Jennings K, Alvarez-Fernandez P, Patel JA, Loeffelholz MJ, et al. Acute Otitis Media and Other Complications of Viral Respiratory Infection. *Pediatrics*. 2016;137(4).
28. Hay AD, Redmond NM, Turnbull S, Christensen H, Thornton H, Little P, et al. Development and internal validation of a clinical rule to improve antibiotic use in children presenting to primary care with acute respiratory tract infection and cough: a prognostic cohort study. *The Lancet Respiratory medicine*. 2016;4(11):902-10.
29. Chonmaitree T, Revai K, Grady JJ, Clos A, Patel JA, Nair S, et al. Viral upper respiratory tract infection and otitis media complication in young children. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2008;46(6):815-23.
30. Stahlberg M-R. The influence of form of day care on occurrence of acute respiratory tract infections among young children. *Acta Paediatr*. 1980;282((suppl)):1-87.
31. Paediatric Formulary Committee. BNF for children. London British Medical Association, Royal Pharmaceutical Society, Royal College of Paediatrics and Child Health, and Neonatal and Paediatric Pharmacists Group;.
32. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International journal of epidemiology*. 2015;44(3):827-36.
33. Hobbs FD, Bankhead C, Mukhtar T, Stevens S, Perera-Salazar R, Holt T, et al. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007-14. *Lancet*. 2016;387(10035):2323-30.
34. van der Velde RY, Wyers CE, Teesselink E, Geusens PP, van den Bergh JP, de Vries F, et al. Trends in oral anti-osteoporosis drug prescription in the United Kingdom between 1990 and 2012: Variation by age, sex, geographic location and ethnicity. *Bone*. 2017;94:50-5.
35. Armstrong D, Ashworth M, Dregan A, White P. The relationship between prior antimicrobial prescription and meningitis: a case-control study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2016;66(645):e228-33.
36. Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R, et al. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ (Clinical research ed)*. 2007;335(7617):429.
37. Thompson M, Vodicka TA, Blair PS, Buckley DI, Heneghan C, Hay AD. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ (Clinical research ed)*. 2013;347:f7027.
38. Shields MD, Thavagnanam S. The difficult coughing child: prolonged acute cough in children. *Cough (London, England)*. 2013;9(1):11.
39. Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. *Jama*. 2005;293(24):3029-35.
40. Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *The British*

journal of general practice : the journal of the Royal College of General Practitioners. 2015;65(639):e702-7.

41. McNulty CA, Nichols T, French DP, Joshi P, Butler CC. Expectations for consultations and antibiotics for respiratory tract infection in primary care: the RTI clinical iceberg. The British journal of general practice : the journal of the Royal College of General Practitioners. 2013;63(612):e429-36.

42. Redmond NM, Thornton H, Turnbull S, Christensen H, Blair PS, Peters TJ, et al. Parent-reported consumption of antibiotics prescribed for children's cough and respiratory tract infections in primary care and factors associated with adherence -analysis from the TARGET study. General Practice Research on Infections Network conference; 2-3 October; Galway 2015.

43. Butler CC, O'Brien K, Pickles T, Hood K, Wootton M, Howe R, et al. Childhood urinary tract infection in primary care: a prospective observational study of prevalence, diagnosis, treatment, and recovery. The British journal of general practice : the journal of the Royal College of General Practitioners. 2015;65(633):e217-23.

44. Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners. 2002;52(478):401-9.

Page left intentionally blank

Chapter 6 Parents' perceptions of antibiotic use and antibiotic resistance (PAUSE): a qualitative interview study

6.1 Introduction

In chapter 5, a substantial UK primary care database (CPRD) was analysed to explore what routinely collected data could tell us about antibiotic use in preschool children and the potential impact or consequences of unnecessary antibiotic use. This showed that children who received more antibiotic courses were more likely to have a subsequent respiratory tract infection (RTI) that did not respond to antibiotic treatment (termed antibiotic “response failure”).

However, in the absence of routine microbiological sampling in primary care, antibiotic resistance is just one possible explanation for clinical “response failure” in primary care. One of the limitations of routinely collected data discussed in Chapter 5 is that the underlying reasons for an association between antibiotic exposure and antibiotic “response failure” are multifactorial, and not necessarily related to the prescribed antibiotic or bacteria. So, for example, for parents and young children, these may include: patient behaviour (e.g. parents have a low threshold for consultation); infection susceptibility of the child; and/or social and environmental factors where transmission of micro-organisms is high (e.g. child attends day care, young siblings at home).

Chapter 2 highlighted that the public have misconceptions about antibiotic resistance and do not perceive a link between resistant bacteria and antibiotic use. This is reflected in disappointing results from national antibiotic awareness campaigns. Yet the role of antibiotics and their benefits and harms, have not been fully explored with parents of young children where so much unnecessary antibiotic use occurs. So, for example, how might the issues that matter to parents and their young children influence the way they use health care services in the UK, or heed public antibiotic awareness messages aimed at them? Insight into these experiences will give us a better understanding of the influences on behaviours, the needs and challenges that a future intervention must address to reduce antibiotic consumption.

Chapter 6 will therefore explore these factors by exploring parents' experiences of caring for their child when they have an acute RTI, their decision to consult their health professional, their beliefs about antibiotic use and how the risk of antibiotic resistance might affect their decision to use antibiotics.

6.1.1 Parents' experiences of managing their child's illness

Young children are commonly seen in primary care for RTIs (1, 2), and it can be difficult for parents to judge when to seek care.(3, 4) Research has generally focussed on parents' views of managing their child's acute RTI, their health-seeking behaviour and the many factors parents weigh up before consulting.(3-9) Parents commonly reported feeling concerned about particular symptoms and/or experienced uncertainty about whether an illness was severe or not.(3, 4, 8) Their ability to assess the severity of the illness appeared to be related to the child's level of distress rather than symptom severity (4), and was influenced by previous experience of similar illnesses (7, 9), or lack of experience if they were first-time parents.(4) Parents also had concerns about whether their child's illness could be managed at home, and perceived that home management may be failing if infections continued for longer than expected.(6) Certain social factors also influenced parents in caring for young children (4-7), for example, parents seeking advice from family and friends as to how to care for their child and receiving guidance from other sources whom they trust, such as child care services, who may not be qualified to provide medical advice. Parents often reported feeling reassured after consulting their doctor (4, 7) and some appeared to be happy with a treatment decision whether or not antibiotics were prescribed.(10, 11) Others however, felt more comfortable with an antibiotic prescription. The factors that these studies highlight are important to acknowledge when considering a non-antibiotic approach in general practice, however these studies do not address how parents consider the benefits and harms of antibiotics as they relate to antibiotic resistance specifically.(10, 12)

6.1.2 Parental concern about antibiotics and their potential effects

Previous studies have tried to quantify parental beliefs about the benefits and harms of antibiotics for children with acute RTIs in the form of survey-based questionnaires of parents with young children.(13-20) These quantitative studies reiterate public misconceptions about antibiotic use for common self-limiting infections outlined in Chapter 2. For example, in a cross-sectional survey of over 5,000 parents in Greece, 88% of parents believed that unnecessary antibiotic use drives antibiotic resistance, yet 74% expected to receive antibiotics when a diagnosis of an upper RTI was made even though around three quarters knew that upper RTI were self-limiting.(13) Other surveys from the USA, Finland and the Netherlands indicated that parents were concerned about antibiotic resistance but held similar misconceptions about antibiotic resistance to the general public.(17, 18) For example, a third of parents of young children in Finland and the Netherlands thought that resistance was unlikely to develop if the antibiotic course was completed.(18) A recent telephone survey across Australia of around 400 parents showed that 78% recognised that antibiotics may cause harm but overestimated the benefits of antibiotics to reduce symptom duration of acute otitis media, sore throat and acute cough by 5 to 10 times, and believed they reduce the likelihood of complications.(21) There have been no such published surveys of parents in the UK. Their views have been subsumed in large household surveys across England, Wales and Scotland or other surveys.(22, 23)

These types of studies can be useful when there is a need to obtain general information about public health knowledge regarding treatment and prevention practices. However, they are limited because the views of responders may not reflect those of the general population because of sampling strategy e.g. convenience sampling (16, 17), recall bias of the child's illness episode and antibiotic use (21), level of literacy and education, or parents' knowledge, attitudes and practices not put into context nor reflecting parents' actual behaviour.(13, 21)

In comparison to quantitative studies, qualitative methods like focus group discussions or in-depth interviews, seek to understand and interpret meaning of the phenomenon under study, and recognise the context in which data is collected providing a detailed and complex account from

each participant yet accommodating and exploring difference and divergence. More widely, qualitative approaches also explore how people interact with their environment and social systems and how these wider contexts may restrict or support particular behaviours.

There are relatively few qualitative studies with parents of young children specifically exploring their views of antibiotic resistance.(15, 24-27) Most of the qualitative research exploring views of antibiotic resistance to date has involved adults regarding their own health and has been carried out outside the UK.(28) The few qualitative studies carried out with parents in the USA, Sweden and Hong Kong suggests parents are concerned about “antibiotic resistance”(24-27), although not all studies.(29) Although one older study involving focus group discussions with parents, suggested that some parents want the “big guns first” (i.e. broad-spectrum antibiotics) so that they didn’t have to come back (26), parents in other studies generally expressed the desire to use antibiotics only when necessary.(24, 25, 27, 29) However, the same misconceptions about antibiotic resistance were evident. For example, parents mistakenly thought that children could become permanently resistant to the antibiotic (24); that the human body develops resistance to the antibiotics (27); and that antibiotics could weaken the body’s resistance, or impair the immune system.(25, 27)

Although parents had a strong desire to be as judicious as possible regarding their antibiotic use (29), parents felt antibiotics were needed for specific symptoms e.g. earache in acute otitis media (24) or in situations where they might accelerate recovery (25), and believed that the repeated use of antibiotics increased the harmful effects of antibiotics.(27) However, despite acknowledging that antibiotics could lead to antibiotic resistance, parents were prepared to give their child antibiotics as they had “no other means to make [their child] feel better” (27), or viewed antibiotics as a “necessary evil”.(29) In a recent study from the USA, very few parents expressed any concerns about antibiotic resistance directly affecting their family but would only become concerned about resistance if their child received antibiotics frequently.(29)

Recent qualitative work from the UK reaffirms that parents have a poor understanding of antibiotic resistance, believing that it is the individual who developed resistance to antibiotics, as opposed to the bacteria or that antibiotics could hinder the development of a child's 'natural' immune response.(30) Two ongoing primary care research studies in the UK are exploring parents' experiences of caring for children with existing medical conditions being unwell with influenza-like illness, including the harms and benefits of antibiotics (31), and parents' perspectives on antibiotic use in children with lower respiratory tract infections in primary care in the context of a larger trial.(32)

No studies to date have focussed on parents' perceptions of the role of antibiotics and the potential significance of antibiotic resistance when caring for a child with an uncomplicated RTI in the UK, nor have any studies explored what strategies parents would find acceptable to minimise antibiotic resistance for themselves, and for their children.

6.1.3 A bottom-up approach to improving antibiotic stewardship

Incorporating parents' current beliefs and understanding about antibiotic use and antibiotic resistance into any new intervention will provide a grassroots resource for other parents with young children. As discussed in Chapter 2 (2.6 Antibiotic awareness campaigns), this is important to inform a bottom-up approach to improve antibiotic stewardship in the community.(33)

Addressing parental misconceptions about antibiotic resistance, and breaking the cycle of inappropriate antibiotic prescribing and use is critical to improving future antibiotic awareness campaigns.

Interventions based on behaviour change theories have successfully reduced inappropriate antibiotic prescribing in hospitals and shown that lower use of antibiotics in these settings probably does not increase mortality and likely reduces length of stay.(34-36) Behaviour change interventions in primary care have also had success in reducing unnecessary antibiotic prescribing. (37) The effect of such interventions has generally been modest. For example, based on 30 trials prior to 2007, the median reduction in the proportion of participants receiving

antibiotics was 9.7% [IQR 6.6–13.7%]).(37) These have usually taken the form of clinician-targeted interventions and patient education, computerised clinical decision support, audit of antibiotic prescribing with feedback of results, or a combination of these interventions and have commonly focussed on acute respiratory tract infections.(38) Modelling public antibiotic awareness campaigns on similar behaviour change theories may therefore also increase their success.(39-41)

Social cognitive theory suggests that people will change their behaviour if they feel the personal benefits of doing so will outweigh the costs ('outcome expectations'), and if they feel confident that they can carry out the desired behaviour ('efficacy expectations').(40) For example, clearly quantifying for patients the risks versus benefits of using antibiotics for self-limiting illnesses may make taking antibiotics a less desirable option. Additionally, educating patients about self-management strategies and potential indicators of serious illness may give them more confidence in looking after their children with fewer antibiotics.(42)

Other frameworks have also been proposed for promoting more appropriate public behaviour in relation to antibiotic use. These include "social marketing" (43, 44), "antibiotic-mainstreaming" (45), and Leventhal's theory of self-regulation.(46) The application of such frameworks to address unnecessary antibiotic use, suggest that the consequences of antibiotic resistance need to be communicated in terms of outcomes which people feel are relevant, tangible and noticeable within a relatively short timeframe. Examples of such outcomes which are likely to be meaningful to parents include the likely illness duration (47, 48), and the chance of antibiotic treatment failure.

Qualitative work has informed the development and evaluation of many behaviour change interventions in adults and children to reduce antibiotic prescribing (49-54), but not all.(55, 56) For example, de Bont et al. explored experiences of Dutch parents when visiting their GP out-of-hours services with their febrile child.(6, 52) They found that parents lacked confidence in self-management strategies and wanted reassurance from health professionals in out-of-hours and

incorporated these factors in a written information booklet for parents on self-management strategies for current and future fever episodes.(52)

Another example is the recent National Institute for Health Research (NIHR)-funded ‘TARGET’ Programme Grant for Applied Research aiming to improve the quality of care given to children presenting to primary care with respiratory tract infections. Qualitative research within this substantial body of work found that communication within consultations often failed to meet parents’ needs: information on symptom relief was lacking, safety-netting advice was too vague to be useful and parents’ concerns went unaddressed.(7, 30, 57) They also found that clinicians wanted information to help them identify the children at risk of deterioration.(5, 58) This led to the team to derive a prognostic rule (*STARWAVE*) using symptoms, signs and demographic characteristics to predict hospitalisation in the following 30 days among children presenting to primary care with acute cough and RTI.(59, 60)

Improving public-targeted communication interventions to promote self-care using non-antibiotic strategies requires that key issues and uncertainties about the impact of antibiotic resistance in the community are addressed. For example, the consequences of taking antibiotics inappropriately need to be more direct, tangible and personally relevant as demonstrated in Chapters 4 and 5. Some would consider that any successful public behaviour change initiative requires that patients consider future antibiotic resistance when deciding how to manage their illness and the appropriateness of the management plan.(61) However, whether it is necessary for people to understand the concept of antibiotic resistance to reduce antibiotic use, as opposed to merely accepting it, is unclear. There have been other public health approaches that have been successful in changing social norms without the need to consider the long-term consequences e.g. recycling and waste disposal. Only through using a qualitative approach will we be able to understand the meanings that parents assign to terms such as “antibiotic resistance”, and identify whether they see it as personally relevant to them and their family.

6.2 Aims and objectives

6.2.1 Aim

To explore parents' perceptions and understanding of antibiotic use and resistance when considering how to manage their young child with an acute respiratory tract infection (RTI)

6.2.2 Objectives

- i. To explore what parents and carers consider to be important when considering antibiotics for their children with respiratory tract infections
- ii. To explore parents' knowledge and understanding of antibiotic resistance
- iii. To explore parents' views on the impact of antibiotic resistance for themselves, and for their children
- iv. To explore what strategies parents would find acceptable to minimise antibiotic resistance for themselves, and for their children

6.3 Methods

6.3.1 Study design and justification

I conducted a qualitative study involving narrative and semi-structured face-to-face interviews with parents of preschool children who recently had an acute RTI (e.g. cough, sore throat). (62, 63)

A narrative approach allowed parents to tell the story of their experience of caring for their child and attending a primary care health care setting with their ill child (where relevant). This approach also provided context on how parents viewed the role of antibiotics and the perceived risk of antibiotic resistance when their child was unwell. Indirectly this also provided an introduction to the more difficult concept of 'antibiotic resistance' as highlighted by my patient and public involvement (PPI) feedback (see 6.3.4).

A qualitative approach was required to achieve an in-depth understanding of the complexities involved in exploring parents' perceptions of the role of antibiotics in the context of their sick child.(64) Face to face, semi-structured interviews were selected as the mode of data collection to explore the experiences of participants and the meanings they attribute to them.(65) This involves researchers encouraging participants to talk about issues pertinent to the research question by asking open-ended questions, usually in one-to-one interviews.

Although there were other candidate qualitative methods that had potential to provide answers to the research question (e.g. focus group discussions), individual semi-structured interviews were chosen to capture the personal experiences of parents' understanding of antibiotic use and resistance and individual interpretations of antibiotic campaign messages in contrast to the shared understandings obtained through focus group interviews. Individual interviews with parents would also allow parents to talk about sensitive issues related to their family.(65)

6.3.2 Participants

Parents or carers, aged ≥ 18 years, included any primary caregiver of the child, e.g. parent, adoptive parent, step-parent. Participants had to have a good standard of spoken English in order to take part, and be willing and able to give informed consent for participation in the study. Three parent groups were sought to compare parents' views: (a) parents who did not attend a primary care or ambulatory health care facility (e.g. GP/ walk-in centre/emergency department) when their child had a RTI, (b) those who consulted in primary or ambulatory care and were prescribed an antibiotic, and (c) those who consulted but did not receive an antibiotic prescription.

A preschool child was defined as a child aged between 6 months and 5 years inclusive. We excluded children younger than 6 months because of the immune protection provided by maternal antibodies transferred from mother to offspring during the first six months of life. A child with a RTI was defined as parent-reported symptoms consistent with a recent upper or lower RTI (e.g. cough, sore throat) within the last 3 months, so that parents could recall the illness episode.

Participants had the freedom to talk about previous illness episodes if they wished. Children with hospital-acquired infection or serious underlying conditions (e.g. cystic fibrosis, immunocompromised) were excluded as these children often require specialised antibiotic treatment strategies.

6.3.3 Recruitment

Parents were actively sought through a number of recruitment strategies. In order to identify participants from the three parent groups outlined above, there were two main recruitment methods.

First, I enlisted the help of general practices across the Oxfordshire CCG. Practices were selected based on their locality (urban vs semi-rural), level of social deprivation and antibiotic prescriptions per practice list size to reflect the social variation of potential participants, and the antibiotic prescribing practices in their locality (Appendix 19). Participating practices were given a briefing about the proposed study, and posters and promotional material advertising the study were made available in GP waiting rooms (Appendix 20). Practices were asked to identify participants during routine consultations with either a GP (general practitioner) or nurse practitioner. Participants were provided with promotional written information about the study (Appendix 20) by their health practitioner and asked to contact the research team directly if they were interested in taking part.

Second, to identify those parents who may not have attended a health care facility, participants were also identified through other community networks. This was predominately through local parent groups and through online advertising platforms. I contacted local baby/toddler groups around greater Oxford listed online (<https://www.oxfordshire.gov.uk/cms/content/toddler-groups>) and attended their groups, inviting participants to participate and/or advertise the study to their friends and extended family. During these visits, I spent between 45 minutes to 1 hour each time inviting participants to the study and handing out promotional material (Appendix 20). All but

one group had at least 20 parents or carers in attendance. Participants were invited to sign-up and contact the chief investigator directly. At the time of signing up online, parents had access to the participant information leaflet (Appendix 21). The study was also advertised through social media (Facebook; fortnightly Twitter feed, University department website; the Clinical Research Network of the National Institute for Health Research) and online advertising platforms (www.mumsnet.com).

Recruitment of parents was directed by the characteristics of previous recruits and based on the characteristics listed in the study protocol (parent's age, child's age, number of children in family and ethnicity of child).

A maximum variation, purposive sample of parents or carers of young children were sought to interview across the greater Thames Valley region over the 2016-7 winter.⁽⁶⁴⁾ By maximum variation sampling, both typical and exemplary cases of parents were actively selected to reflect parents' diverse experiences.⁽⁶⁶⁾ Purposeful sampling used in qualitative research involves using the most effective use of limited resources to identify and select individuals that are especially knowledgeable about or experienced with a phenomenon of interest (67, 68), their availability and willingness to participate, and the ability to communicate experiences and opinions in an articulate, expressive, and reflective manner.⁽⁶⁹⁾ This sampling method was chosen to generate sufficient rich data (see 6.3.6 Data sampling and saturation) whilst reflecting parents' diverse experiences.

I was mindful that other common sampling strategies were available and that invariably there is some overlap between sampling strategies. However, the relative balance is dependent on the research question and the chosen style of data analysis and interpretation.⁽⁷⁰⁾ Some sampling strategies were not appropriate. For example, convenience sampling i.e. selecting parents because they are accessible to the researcher, may have been much easier and quicker to complete. However, convenience sampling does not necessarily bear any relationship to the wider parent population, would require more participants and is considered to be the least rigorous and

justifiable sampling method.(71) Using theoretical sampling, commonly employed in grounded theory, was also not applicable to my study because I was not selecting a new sample based on interpretative theories.(70)

To achieve a satisfactory response rate in the time available, I had to be open to other sampling strategies. Firstly, sampling participants through the “snowballing” technique whereby parents could recommend other parents as potential candidates for the study was used.(72) This strategy is an efficient method to access a target population and may reach parents that are difficult to sample such as working moms. I was however mindful that by using snowballing there is a risk of oversampling a particular network of parents with the same perceptions leading to sample bias. Secondly, to ensure diversity of parents, family size and their health-seeking behaviour, I also used a measure of stratification sampling according to the age of participant, number of children, whether they attended a health facility or not, and if they attended, whether their child was prescribed an antibiotic.(73) The advantage of stratification sampling ensures that the range and diversity of different groups in the population are included in the sample.(73) However, the main disadvantage of sampling participants according to specific subgroups is that the researcher pre-emptively identifies different types of people that make up the target population.

6.3.4 Patient and public involvement (PPI)

I enlisted the help of two PPI representatives who provided feedback on the design of the study, the study protocol and further development of the study. One PPI advisor (Mrs Jennifer Bostock) had extensive experience of PPI and research on infections and antibiotics. She is an HCAI (Healthcare-associated infections) Service Users’ Research Forum member and lead reviewer for an NHS Research Ethics Committee. She specifically highlighted some of the potential ethical issues that may arise in the study, which I addressed in my funding and ethics application. My second PPI advisor (Mrs Jean Simmonds) is a patient representative from the National Institute for Health Research (NIHR) Patients Active in Research (PAIR) Thames Valley group. She highlighted that the concept of ‘antibiotic resistance’ was challenging for lay people to understand

and advised on interview strategies to address this challenge. She also helped clarify the wording and structure of the plain English summary in my funding and ethics application, and provided input on the development of the interview guide.

6.3.5 Data collection

The interview topic guide was piloted with a mother of a preschool child prior to data collection. Based on the feedback I received from my supervisor (STC), I learned to purposively leave more periods of silences before moving to the next question to encourage parents to say more and to acknowledge their beliefs whether they were medically correct or not. Topics covered in the interview guide included:

- i. Perceptions and experiences of seeking advice for their child with an acute RTI
- ii. Beliefs regarding benefits of antibiotics versus concerns about their potential harms
- iii. Awareness and understanding of antibiotic resistance and its potential implications
- iv. Views on risk communication about antibiotic resistance
- v. Experiences and perceptions of the impact of antibiotic-resistant infections on themselves, their children, other household members and the wider community
- vi. Views on what would influence their own behaviour in relation to antibiotic use for their child.

Interview questions under each topic were informed by existing topic guides from previous studies (9, 15, 24-27, 57, 74), and Social Cognitive Theory and other theoretical behaviour change theories.(40, 46) The use of theory ensured that questions asked about likely determinants of parent behaviour, and included questions about parents' perceptions of attitudes of significant others (e.g. family and friends) and beliefs about confidence in carrying out specific behaviours (e.g. self-care of RTI).

I amended the interview guide after the initial set of interviews to incorporate new topics which occurred spontaneously during interviews. This was an iterative process, of collecting data,

analysing it, amending the interview guide, and collecting data again. I have specifically highlighted these with a double asterisk in the interview guide (Appendix 22) and indicated when these additional topics were included.

Interviews were conducted at the participant's home or other suitable setting of their preference, and were planned to last between 30-60 minutes. I obtained written informed consent from participants to obtain audio recordings of the interviews; to check they understood the purpose of the study and that participation was voluntary; to give them the opportunity to ask questions; and to use transcribed anonymised quotes from the interview in further dissemination (Appendix 21; Appendix 23). Participants were also made aware that if they were to disclose any information that may cause harm to themselves or others, or relates to criminal activity, then I will have a duty of care to report such information. In such cases a participant's identity will remain anonymous, where possible, and information treated in confidence.

Interviews were digitally audio-recorded, encrypted and uploaded to a secure University website portal (*OxFiles*; <https://oxfile.ox.ac.uk/oxfile>) where an independent transcription service (Transcript Divas Limited) accessed the encrypted files. A transcription confidentiality agreement was set up between the University and the transcription company. Interviews were transcribed verbatim and transcripts were checked for accuracy and anonymised.

In recognition of their contribution, interviewed participants received a £20 gift voucher. All study data were securely stored as per protocol and detailed in the participant information leaflet (Appendix 21).

6.3.6 Data saturation

The prevailing concept of data saturation is a widely used rationale for sample size in qualitative research and typically refers to the point when additional data fails to generate new information.(71, 75) Others have described saturation as where data are collected to provide a complete and truthful picture of the purpose of the study i.e. its credibility is dependent on data

saturation.(73, 76) Data saturation can also be viewed when further coding is no longer feasible.(77) Others have also suggested that “saturation should be more concerned with reaching the point where it becomes counter-productive and that the ‘new’ that is discovered does not necessarily add anything to the overall story, model, theory or framework” as there is always the potential for “the new to emerge”.(78)

However, these principles provide minimal guidance for planning for less experienced researchers, nor provide any clarity on why and how decisions regarding design, sampling and analysis are taken.(79) Therefore, to guide adequate sample size for this qualitative study, I firstly needed to give an approximate number of participants needed, while continuously evaluating the adequacy of the final sample during the study.(80, 81)

I estimated that I would interview between 15-30 participants.(73) This estimate was based on common trends in qualitative research where the sample is appropriate to the research question and theoretical aims of the study (82, 83), other qualitative studies specific to this topic (6, 32, 57, 84) and for pragmatic reasons (e.g. capped funding; time constraints).

I found the analogy “Information Power” of the sample as termed by Malterud et al. a very useful tool to guide my progress throughout data collection and analysis.(80) Information power indicates that the more information the sample holds, relevant to the actual study, the lower amount of participants is needed, and uses a five-item tool to determine the Information Power of the sample. These five items are: (a) study aim, (b) sample specificity, (c) use of established theory, (d) quality of dialogue, and (e) analysis strategy.(80) I applied this model to my study recognising that there is a trade-off between conditions that require more versus fewer participants in a sample, and that there is a dynamic interaction between the different items.

Taking each item in turn, my study aim required a relatively larger sample because parents with young children are a heterogeneous population group with varying parenting skills and many parents (if not all) have had contact with health care services in the community. In terms of specificity, the combination of participants was relatively dense for the study aim. From my

observations at baby/toddler groups, I anticipated that participants would be predominately mothers between the ages of 30 and 40 years old in and around affluent Oxford. This meant that fewer participants would be needed. The study did not apply specific theories for planning and analysis. Therefore, the use of established theory was not applicable. There was clear communication between the researcher and participants requiring fewer participants to offer sufficient information power. I achieved this by: following a semi-structured interview guide, making the quality of dialogue focussed (77); relying on my expert communication skills as a NHS general practitioner to make participants feel at ease; asking participants to clarify their answers or checking my interpretations of their answers; and augmenting my interview strategy by using promotional campaign leaflets in acknowledgement that the concept of ‘antibiotic resistance’ is challenging for lay people to understand. Lastly, I applied a cross-case analysis of parents’ perceptions presenting patterns relevant to the study aim by comparing the three parent groups mentioned in 6.3.2. This required relatively more participants to offer sufficient information power than in-depth analysis of narratives from a few selected participants.

6.3.7 Researcher characteristics and reflexivity

In any qualitative study, the researcher's theoretical outlook, interests and expectations inevitably influence all aspects of the research process.(85) Reflexivity or self-appraisal in research relates to the researcher reflecting on their “situatedness” within their research and the effect that this may have on the setting and people being studied, questions asked, data collected and interpretation.(86) Berger et al. have outlined three areas where researcher position can impact on the research process, namely (a) access to the field – respondents may be more willing to share their experiences with a researcher whom they think is sympathetic or shares their viewpoint; (b) nature of the researcher-researched relationship; and (c) worldview and background of the researcher affecting how he/she uses language, poses questions, and chooses the lens for filtering the information gathered from participants.(86)

Overall, I was particularly mindful that my personal, cultural and experiential background as a clinician would bring in biases and values that could affect saturation.⁽⁸⁷⁾ I therefore applied an iterative approach to data collection and analysis by continuously going through cycles of data collection and analysis until no new perspectives and explanations were coming from the data. To provide balance, and a different set of perspectives, I collaborated with my supervisor (STC) in refining the coding strategy and developing the thematic framework.

I was acutely aware that there were potential biases I might introduce in my dual role as clinician and qualitative researcher.^(88, 89) For example, the interviewing skills needed for clinical history-taking are not necessarily transferable to qualitative interviewing. The goal of the clinical consultation is guided by the clinician's perspective, while the semi-structured interview is intended to elicit the meanings attributed by the participant to a particular research question.⁽⁸⁵⁾ Additionally, there is also the problem of “reactivity”: the potential introduction of bias from participants by giving socially desirable answers to an expert, or alter their answers as they are aware of being studied.⁽⁹⁰⁾ I was able to reduce this bias by addressing this issue upfront prior to the interview stating that I regarded participants (parents) as experts of their children and that there were no wrong answers. Interviews were conducted in participants’ own homes where they were comfortable, often with their young children at home. It was hoped that this would mitigate any power differential felt by participants.

I found my dual role to get me more “buy-in” from potential participants during recruitment, and participants were responsive, open and placed their trust in me (as they normally would during a GP consultation). Although I do not have any children of my own (yet), most of my close friends of similar age do have young families. I have first-hand experience of the difficulties and anxiety that my parent friends have had to go through when looking after their unwell child.

From my clinical interactions with parents of young children, I had preconceptions of what participants might share. I was aware there were inherent power differentials that could affect how I interpreted what parents were saying, or inadvertently shaping responses or distorting

results to fit existing theories.(90) To mitigate this, I was able to bracket my preconceptions sufficiently to accommodate their voice and experiences and let parents tell their story, as experts of their children, using an open-ended, non-judgemental approach to questioning.

6.3.8 Data analysis

As the researcher undertaking all data collection, I analysed all transcripts making comparisons between data across and within interviews iteratively using thematic analysis.(91) My choice of thematic analysis over other analytical techniques was guided by the purpose of the research, my prior experience of qualitative research, and my philosophical assumptions (e.g. relativist vs. realist view). I was drawn to thematic analysis because it can be used within different theoretical frameworks in contrast to methods like interpretative phenomenological analysis (IPA) and its accessibility for novice qualitative researchers like myself.

I was mindful that there were disadvantages of thematic analysis when compared to other qualitative analytical methods. For example, unlike discourse analysis, simple thematic analysis does not allow the researcher to delve into the intricacies or effects of language use.(91) Similarly, a true grounded theory approach (i.e. developing theories that are grounded in the data collected), was methodologically unsuitable here for two reasons: (a) I could not foreseeably conduct my research without tapping into my preconceived ideas or theories about antibiotic prescribing and antibiotic resistance as a practising NHS general practitioner and (b) the aim of my research was not to generate theory, but rather shed light on experiences and behaviours of parents with young children. Another realist approach to analysis that I considered was framework analysis by Ritchie and Spencer (1994).(92) This approach draws on *a priori* issues, and those emerging from the data collection to draw up a framework, and then uses a charting process to display all material relating to individual themes across all participants including gaps where participants for example, do not respond.(93) However I judged this method to be unsuitable in this instance because my clinical knowledge about the topic would unduly influence the direction of the narrative, and compartmentalise themes without truly being data-driven.

Thematic analysis would therefore provide a better balance between the above-mentioned biases and allow a “bottom-up” approach to identify parents’ perceptions of antibiotics and antibiotics resistance.

Thematic analysis is a well described method for identifying, analysing and reporting patterns (themes) within data consisting of six phases: data familiarisation; generating initial codes; searching for themes; reviewing themes; defining and naming themes; and producing the report.(91)

Anonymised transcripts were firstly entered into specialist software (NVivo version 11) to organise data. I then familiarised myself with the data by repeated active reading of transcripts to generate initial ideas or thoughts for coding.

The next phase consisted of systematically producing initial codes from the data using a line by line approach.(94) I gave equal attention to each line to identify the most basic segment or element of data that was meaningful and to identify interesting aspects of the data that may form the basis of repeated patterns (themes) across the data set. Using this inductive or bottom-up approach whereby the process of coding was data-driven without relying on an existing coding frame, mitigated against my analytic preconceptions.(91)

To ensure the quality and balance of the initial codes I identified after 6 initial interviews, a proportion of transcripts were checked against the interview data by my supervisor (STC). Transcripts of interview 5 and 6 were purposefully chosen and checked to reflect the diversity of the interviews in terms of parent gender and diversity of opinion about the role of antibiotics. The value of this exercise of multiple coding and subsequent discussions provided the opportunity to refine existing coding strategies and furnish alternative data interpretations.(95)

After 8 interviews were coded and prior to the third phase (searching for themes), two subsequent interviews (interview 10 and interview 12) were purposively selected from 15 transcripts to provide variation in parent reports of attitudes and knowledge. This was useful to highlight the

tensions and breadth across the data that departed from the dominant story in the analysis and incorporate these in my coding list.

Now, based on 10 coded interviews, I compared and sorted codes into potential themes to create categories, grouping similar codes together to form an initial thematic framework.⁽⁹⁴⁾ I used the OSOP (one sheet of paper) approach to find the common story or pattern in each theme.⁽⁹⁶⁾ This visual representation helped sort the different codes into candidate themes, and draw attention to the relationship between themes and between different levels of themes (i.e. main overarching themes and sub-themes within them).

The fourth phase involved reviewing and refining this coding framework of candidate themes (Appendix 24) to make the final list of themes and subthemes (Table2). This was an iterative process scrutinising that data within themes cohere together meaningfully, and that there were clear distinctions between themes. If there was insufficient data to support themes or data were too diverse, candidate themes were either reworked to create a new theme, or discarded from the analysis as needed. I then applied this refinement process to subsequent transcripts and refined, amended or discarded as needed to test the validity of the individual themes in relation to the entire dataset, and to code any additional data within themes that had been missed in earlier coding strategies.

During the fifth phase, I generated clear definitions and names for each theme identifying the essence of what each theme was about i.e. the “story”, and what aspect of the data each theme captured.⁽⁹¹⁾ Themes and sub-themes were further refined with my supervisor (STC) to give structure to large and complex themes, and to illustrate the hierarchy of meaning within the data.

The final phase involved writing-up my findings with a set of finalised themes to give a concise account of the story the data told within and across themes. I achieved this by giving extracts of the data which captured the essence of the theme (Appendix 25), and embedding these extracts within an analytic narrative rooted to my initial research question.

6.3.9 Quality in qualitative research

There is considerable debate over not only the characteristics that define good quality qualitative research, but also on whether criteria for quality in qualitative research should exist at all.(97)

Quantitative research traditionally uses measures like reliability and validity to judge how accurately data reflect an external ‘truth’. Anti-realists would argue that qualitative research should not be judged by such conventional measures because they reject a single, unequivocal social reality or truth which is entirely separate from the researcher and the research process.

Others would advocate that all research involves subjective perception and that different methods produce perspectives but that there is an underlying reality that can be studied (“subtle realism”) i.e. an attempt to represent that reality rather than to attain “the truth”.(98) Given the plurality of qualitative research at the level of data collection and methodologies, producing a unified set of criteria is difficult but potentially flawed.

Notwithstanding these debates, some means of determining the quality of qualitative studies is needed to ensure rigour in qualitative research. Although frameworks for assessing qualitative research (99) and critical appraisal instruments exist (100), it is unlikely that a checklist of quality criteria would be appropriate, definitive or manageable.(97, 98) It is from this position that I have used a series a prompts developed by a project team in the Economic and Social Research Council (ESRC) Research Methods Programme (Box 1) to ensure rigour and appraise qualitative research.(97) Results are reported according to the Standards for Reporting Qualitative Research (SRQR), as recommended by the Equator Network.(101)

Box 1 Prompts for appraising qualitative research

- Are the research questions clear?
- Are the research questions suited to qualitative inquiry?
- Are the following clearly described?
 - sampling, data collection, analysis
- Are the following appropriate to the research question?
 - sampling, data collection, analysis
- Are the claims made supported by sufficient evidence?
- Are the data, interpretations, and conclusions clearly integrated?
- Does the paper make a useful contribution?

6.3.10 Ethics

Ethical approval was obtained from the Health Research Authority, with reference 16/NW/0779 on 9 November 2016.

6.4 Results

I refined the topic guide three times to incorporate emerging findings from six initial interviews, and additional questions that were researcher-driven. These topics were not included in the original interview guide. I included these additional topics in the interview guide and indicated after how many interviews there were included in the interview guide (Appendix 22). Where appropriate topics explored were: (a) beliefs regarding the advice given by health professionals that antibiotic courses need to be completed in order to improve recovery and to curb antibiotic resistance; (b) the concern of parents about serious illness and the risk of sepsis taking into consideration current national sepsis campaigns (102); and (c) attendance at Accident & Emergency during out-of-hours in light of concurrent research studies (e.g. CATCH study <http://www.hra.nhs.uk/news/research-summaries/catch-parents-and-carers-attending-ae-for-children-with-fever/>).

Data saturation was indicated after 18 interviews. I conducted a further set of five interviews to confirm this.

6.4.1 Participant characteristics

From a sample of 34 participants that showed initial interest in the study, I purposively selected 23 parents. Parents were interviewed between November 2016 and July 2017. Participant characteristics are summarised in Table 1. Two interviews were conducted in the Nuffield Department of Primary Care Health Sciences, University of Oxford with the remainder at parents' homes of which one was via Skype. Interviews ranged from 25 to 52 minutes in duration, with a mean of 37 minutes. Eleven parents were between 25-35 years old; twelve were older than 35

years old with an average age of 35 years old. The majority of parents were female with one child. The average age of the child was around 24 months. Around two-thirds of parents identified themselves as White British. Most parents were recruited through toddler groups in the community (toddler group 4 had no recruits); only one parent was recruited through a GP practice. Around a quarter of parents managed their child's acute RTI symptoms at home. The remaining 17 parents consulted a healthcare professional with their ill child of which nine were prescribed an antibiotic.

Table 1 Characteristics of parents (N=23)

Participant Code	Sex	Age	Child age	No. of children (ages)	Primary complaint of child	Ethnicity	Interview duration (min)	Recruitment method
Recruitment Group 1: Did not attend GP (n=6)								
2	F	39	3yr girl	3; (3,7,9yr)	Acute RTI	British White	52	Toddler Group 1
7	F	33	21m boy	1	Acute RTI	British White	34	Toddler Group 2
10	M	36	16m girl	1	Sinus infection	White Other	29	University email
17	F	33	6m boy	2; (6m,2yr)	Cough	British White	28	Toddler Group 7
20	M	33	2yr girl	1	Cough	British White	45	Toddler Group 3
23	F	38	18m boy	1	Cough	British White	34	Toddler Group 6
Recruitment Group 2: Attended GP and not prescribed antibiotics (n=8)								
3	F	35	2.5yr girl	1	Recurrent URTI	White Other	37	Toddler Group 1
5	F	39	2yr boy	3; (2,4,7yr)	Chest infection	British White	43	Toddler Group 1
11	F	33	20m boy	1	Persistent cough	British White	28	Facebook
12	F	34	2.5yr boy	1	Persistent cough	White Other	22	Toddler Group 2
13	F	33	15m girl	1	Cough	British White	43	Toddler Group 5
14	F	35	2.5 girl	1	Cough	White Other	34	GP Practice 1
15	F	36	11m boy	4; (11m,6,8,10yr)	Cough	British Other	25	Toddler Group 5
16	F	35	6m girl	2; (6m,3yr)	Cough	British White	36	Toddler Group 6
Recruitment Group 3: Attended GP and prescribed antibiotics (n=9)								
1	F	36	10m boy	1	Recurrent URTI	British White	39	University email
4	F	36	19m boy	2; (19m,10wk)	Ear infection	British White	52	Toddler Group 1
6	M	40	5yr girl	1	Ear infection	White Other	36	Research Network
8	F	36	3yr boy	1	Tonsillitis, cough	British White	50	Facebook
9	F	29	4yr girl	2; (2,4,6yr)	Ear infection	Asian	36	Snowball
18	F	37	2yr boy	3;(2,3,4yr)	Chest infection	British White	42	Toddler Group 8
19	F	39	3yr boy	1	Chest infection	British White	35	Snowball
21	F	39	12m boy	1	Ear infection	Mixed race	34	Snowball
22	F	34	18m boy	2; (18m,3.5yr)	Chest infection	Mixed race	44	Snowball

6.4.2 Qualitative findings

Eight themes were generated from the data (Table 2). Each theme is illustrated with quotations from parents, identified by participant code, recruitment group, age of child, and number of children.

Table 2 Main themes and subthemes

Theme 1 Parents' experiences of managing RTIs in their children 1a. Parental concern regarding child's symptoms 1b. Parents' sources of advice and treatment strategies at home
Theme 2 Parents' experiences of consulting the GP for treatment 2a. Parents' decision about consulting their GP 2b. Perceptions of GP management and access to healthcare 2c. Perceived appropriateness of antibiotics at GP
Theme 3 Uncertainty about the risks of antibiotics and their use 3a. Perceptions of harms of antibiotics 3b. Perceptions and experiences of benefits of antibiotics 3c. Perceptions of how and when antibiotics are used
Theme 4 Parents' understanding of antibiotic resistance 4a. Description and knowledge of antibiotic resistance 4b. Frequent antibiotic use and inappropriate behaviours contribute to antibiotic resistance
Theme 5 Perceived consequences of antibiotic resistance 5a. Implications of antibiotic resistance for patients 5b. Impact of antibiotic resistance on close family 5c. Healthcare implications
Theme 6 Ways to reduce antibiotic resistance in response to campaign materials 6a. Healthy lifestyle choices to reduce antibiotic resistance 6b. Prudent use of antibiotics
Theme 7 Parents' reflections on current antibiotic awareness materials 7a. Perceived personal relevance of campaigns 7b. Perceptions of enablement of campaign messages
Theme 8 Social responsibility to inform parents about antibiotic resistance 8a. Better communication about antibiotics and resistance, and diagnostic tools during consultations 8b. Better public campaign strategies on antibiotic resistance in terms of content, timing, and targeting populations

Theme 1: Parents' experiences of managing RTIs in their children

1a. Parental concern regarding child's symptoms

Parents expressed a range of experiences in caring for their sick child before consultation with a healthcare provider. Parents generally accepted that children were prone to getting minor illnesses and some parents were quite comfortable dealing with their child's symptoms.

"He did [have fever]. It wasn't a high temperature. It was kind of 38-ish. 38.5, which we thought, 'Oh, stick some Calpol in him, he will be fine'."

(P19; recruitment group 3, one child aged 3 years old)

Illness duration was a concern for some but not all parents and not necessarily because of their fear of serious illness.

"No, [the cough was not different] it was just because it stayed for so long so I hadn't had the feeling for a long time that it's getting better, normally with a cold, after a week or so you can see it's getting better"

(P12; recruitment group 2, one child aged 2 years old)

"I think he coughed for about three weeks, but it wasn't a bad cough [...]. It just took a long time to get over it. I don't think I was worried. I was only worried at night when he was [troubled by] the phlegm. I was more worried about [him] not sleeping and about him being traumatised from it. I wasn't worried about anything bad happening to him"

(P5; recruitment group 2, three children aged 2, 4 and 7 years old)

However, some parents worried about serious illness that might lead to sudden deterioration and felt that antibiotics would prevent emergency hospital admission. Parents also voiced their concerns that some infections were "hidden" and needed expert advice.

"I mean some infections are really visible and some are more hidden, but I guess the hidden ones are the ones that you need diagnosis on and you need an expert [...]."

(P4; recruitment group 3, two children aged 19 months and 10 weeks)

"I think my mind probably went to the worst possible scenario that it was a serious chest infection or fluid on her lungs or it could've been anything really. But yes, I don't know that there was any logical explanation for my concerns it was just what if it's something more serious."

(P13; recruitment group 2, one child aged 15 months)

1b. Parents' sources of advice and treatment strategies at home

Parents sought advice through several avenues, often concurrently: family members, other parents, pharmacists, health visitors, NHS websites and internet search engines. They used a variety of strategies to nurse and comfort their child before seeking medical help but were either unsure or sometimes frustrated about what to try or whether it would help.

"Sometimes I will Google and go to sites like Mumsnet and look at people's discussions. I don't add to them but [...] often, you can find quite useful stuff because it's just people's experiences."

(P17; recruitment group 1, one child aged 6 months)

"We had vapour rubs, steam, we were recommended to go into a steamy room. Well, try that with a ten month old baby that wants to fidget, always screaming and was coughing at two o'clock in the morning, it is very hard to do those things, especially when you have other children sleeping in the house as well."

(P18; recruitment group 3, four children aged 11 months, 6, 8, 10 years old)

Theme 2: Parents' experiences of consulting the GP for treatment

2a. Parents' decision about consulting their GP

Parents that did consult their GP did so for reassurance that their child's illness was not serious. Some consulted based on advice from a third party (e.g. nursery). One parent wanted early intervention by the GP perceiving that this could speed up their child's recovery.

"So we went to the GP just to have a look and let us know what's going on. Obviously, I wasn't expecting antibiotics or anything. I just went to see [the GP] to double check [...] I think the GP told us to get paracetamol and wait it out and she was eventually better."

(P14; recruitment group 2, one child aged 2.5 years old)

"It was honestly because nursery [advised us to go]. They said, you know, 'We think you should go and see a GP'. And they deal with lots of children every day and have seen more sick children than I have, so I kind of trusted their judgement."

(P19; recruitment group 3, one child aged 2 years old)

“I was happy [that child was seen by the GP]. I think when it comes to the care of a child [...] I want the best, most effective remedy as quickly as possible for my child to get back to a normal health level.”

(P6 father; recruitment group 3, one child aged 5 years old)

Parents that did not consult their GP acknowledged that not all RTI symptoms warrant to be seen in the clinic unless the symptoms were perceived to be unusual or severe.

“We didn't feel like we needed to [go see the GP]. We've called 111 a couple of times about other things in the past and I think we feel like we probably don't need to see a GP unless it's something that we feel is very unusual or very severe. Now that she is two, I think we are familiar with what is severe and what a run of the mill infection is.”

(P20 father; recruitment group 1, one child aged 2 years old)

2b. Perceptions of GP management and access to healthcare

Parents perceived GP practices to be responsive to the needs of parents caring for their ill child. Parents, overall, were satisfied with the diagnostic evaluation and advice given by healthcare providers. Where parents could not get an early appointment, some were prepared to wait to be seen by a healthcare provider provided the symptoms were not perceived to be serious or severe. One parent (P13) commented that they hadn't really built up any kind of relationship with their GP and preferred to see the practice nurse.

“It's reassuring having a GP check your child over to ensure there's no bacterial infection, and that's reassuring and I'm really grateful for the NHS GPs to be doing that”

(P6 father; recruitment group 3, one child aged 5 years old)

“When he was coughing for about three weeks [and] I couldn't get an appointment with my GP for one and a half weeks, so I just waited until he was free because it wasn't that bad.”

(P12; recruitment group 2, one child aged 2 years old)

Parents recognised that NHS resources were stretched. They valued the reassurance that GPs provided and had confidence in their expertise. However, some parents felt ambivalence and powerless that clinicians were so busy and might miss something. The examination of the child appeared to be important in reassuring parents.

“I felt like [the child examination] was thorough and we had specific questions and that’s what [the GP] focused on and it was helpful. We went there for reassurance and that’s what we got basically.”

(P11; recruitment group 2, one child aged 20 months)

“I guess you have to be sure that you are confident with the GP’s advice, and sometimes that is a bit of a concern if they are rushed, and you don’t know if they are looking properly, and I imagine they are very experienced.”

(P1; recruitment group 3, one child aged 10 months)

A few parents vented their frustration that there was seemingly not much more that could be done without antibiotics implying that antibiotics might be helpful to relieve pain.

“It makes you quite uneasy [when antibiotics are not prescribed], because there is nothing else you can do, and Calpol doesn’t really help that much. It helps alleviate the temperature and slight pain, but there is nothing else you can do, and as a parent you do worry that they are in pain.”

(P1; recruitment group 3, one child aged 10 months)

2c. Perceived appropriateness of antibiotics at GP

Most parents did not expect antibiotics for their child’s symptoms. Parents felt that GPs were not prescribing antibiotics as liberally as in the past, akin with their own reticence for antibiotics.

Parents placed their trust in their clinician to make the correct call about whether antibiotics were needed.

“Like the GP we now have, [...] I trust her to make the right call whereas I guess if you had a GP that you didn’t trust, then maybe you would pursue a different course or you would ask for a second opinion.”

(P13; recruitment group 2, one child aged 15 months)

“[GPs are not] just dishing out antibiotics for no good reason. So if that’s what they recommended, then, you know, I just have Dr Google as my training, so I trusted their [GPs] judgement.”

(P19; recruitment group 3, one child aged 3 years old)

Some parents were wary of using antibiotics for their child too readily. They expressed their uneasiness about trusting the GP prescribing antibiotics and felt powerless to resist antibiotics.

They would like to be a position to discuss the appropriateness of antibiotics for their child with their GP.

“I don’t want to just chuck antibiotics down my son’s neck for the sake of it. I hope I did the right thing [...] but if I go and [the GP] says he needs antibiotics, I’d like to be in a position where I can ask more about that, and just have a little discussion about that before I say yes or no. I don’t know if I could say no to a GP, that’s the thing, you know, they’re supposed to be the experts.”

(P4; recruitment group 3, two children aged 19 months and 10 weeks)

Lastly, some parents described antibiotics as a means to ease the pressures of modern day family life where parents need to work and children attend nursery. Interestingly, one parent thought that self-treating strategies were more difficult to trust in an era where the public had access to (often unvetted) information.

“I know that if she’s ill she cannot sleep and that disrupts my own peace of mind and my wife’s, and sleep, and our attitude to life and work the next day.”

(P6 father; recruitment group 3, one child aged 5 years old)

“There’s a few [nurseries] where if they’ve had the antibiotics then they’re allowed to attend playgroup or they’re allowed to do things. So that’s definitely a bonus.”

(P2; recruitment group 1, three children aged 3, 7 and 9 years old)

“I think self-treating has almost become less popular, and to treat a non-serious problem, people probably worry more almost because they know more.”

(P17; recruitment group 1, one child aged 6 months)

Theme 3: Uncertainty about the risks of antibiotics and their use

3a. Perceptions of harms of antibiotics

Parents associated the potential harms of taking antibiotics with side-effects of taking any medication. These side-effects ranged from minor ailments like thrush and gastrointestinal upset, to more severe side-effects like an allergic reaction.

“Yes, I guess a bit like any drug, [antibiotics] come with a list of possible side effects and I know they have to put every possible side effect that’s come up in trials so it doesn’t make for a particularly nice reading.”

(P13; recruitment group 2, one child aged 15 months)

Many parents were aware that antibiotics changed the gut bacterial flora and “kill off the good bacteria”. Some parents perceived this change to relate to the potential to develop chronic conditions later in life.

“Because my side of the family are very prone to eczema and asthma, I thought [antibiotics] could increase [my child’s] risk of complications later in life, because he is already at a small risk anyway, due to genetics.”

(P1; recruitment group 3, one child aged 10 months)

However, a handful of parents were unaware of any side-effects or risk associated with antibiotics. Others were unsure about the consequences or harms of antibiotics long-term or simply downplayed this risk because antibiotics had undergone rigorous testing in children.

“I’ve never been one for shying away from medication and if it’s there, it’s been tested, I’m sure it’s fine. [...] Do you know, I don’t even think about antibiotics as risky.”

(P2; recruitment group 1, three children aged 3, 7 and 9 years old)

Four parents had unusual perceptions about the effect of using (or not) antibiotics on the immune system.

“Because she’s still young and I think that if it’s something that she can fight it off, it will help her in the long run [...]. If I start pumping her with antibiotics she will have a weak immune system.”

(P14; recruitment group 2, one child aged 2.5 years old)

“And certainly, I feel like it’s also probably good for her overall health to get several colds [without antibiotics], it boosts her overall immunity.”

(P13; recruitment group 2, one child aged 15 months)

Only a minority of parents linked antibiotic resistance (or their interpretation thereof) as a potential harm of antibiotics. Only six parents mentioned antibiotic resistance as a possible harm of antibiotics of which two had consulted their GP.

“Resistance is a big [potential harm], so it’s not to be taken lightly, especially with the over usages [of antibiotics] that we’re getting now, we’d only use them in ... if it was absolutely needed.”

(P10 father, recruitment group 1, one child aged 16 months)

“But I think maybe if you’re getting [antibiotics] too much then you cannot do anything because then you’ve lowered your resistance.”

(P14; recruitment group 2, one child aged 2.5 years old)

3b. Perceptions and experiences of benefits of antibiotics

In contrast, all parents could readily explain the benefits of antibiotics and relate this to personal experiences of their child making a speedy recovery.

“...I do see [antibiotics] as this thing that’s a really quick prescription, a really quick fix, but then, when you’re in the moment of someone that you really love being really unwell then if it’s going to fix them and make them feel 100 times better within a couple ... I think it was literally, like, the next day he was already 90% himself. Antibiotics are amazing.”

(P4; recruitment group 3, two children aged 19 months and 10 weeks)

Although a few parents perceived that antibiotics might weaken the immune response (3a Perceptions of harms of antibiotics), some parents viewed antibiotics as an adjunct to help the immune system ‘finish off’ an infection, while other parents thought that antibiotics prevented infections from becoming more severe.

“Advantages, I always think it’s just a case of getting something over, getting the illness over and done with more quickly, so kind of helping your immune system to finish it off.”

(P2; recruitment group 1, three children child aged 3, 7, 9 years old)

3c. Perceptions of how and when antibiotics are used

Parents all agreed that antibiotics are used to treat infections but did not readily make the distinction between viral and bacterial infections. Only a minority were aware that antibiotics are also used in other facets of medicine e.g. chemotherapy and antibiotic prophylaxis.

“So, if someone has a fever and pain somewhere specific, so I guess the signs of infection, then you would need [antibiotics] before you got more poorly.”

(P11; recruitment group 2, one child aged 20 months)

Some parents attributed the need for antibiotics on perceived symptom severity even though symptoms or symptom severity might not be attributable to a bacterial infection.

“If they were in a lot of pain, if they had a very high temperature, if they were not themselves at all, you know, just lying around and not having much energy to jump around and stuff, then I would think [they would need an antibiotic].”

(P16; recruitment group 2, two children aged 6 months and 2 years old)

“It might depend on [symptom] severity, whether it needs treating or not, but it still might not be caused by a bacterial infection anyway.”

(P17; recruitment group 1, one child aged 6 months)

However, a handful of parents underestimated the duration of self-limiting RTI illness and thought that antibiotics were needed if children had prolonged symptoms in their opinion.

“I think if it’s a sore throat for example, perhaps [antibiotics] would help to reduce the amount of time that sore throat goes on for. So, if it was to continue for a week, it may just help clear it within four or five days, rather than it wouldn’t particularly alleviate the symptoms that much.”

(P1; recruitment group 3, one child aged 10 months)

Parents were more certain about antibiotics and their use for serious infections like sepsis, meningitis, or other localised infections (e.g. tonsillitis). However, very few parents realised that only a small proportion of infections, including some bacterial infections, actually need an antibiotic.

“[Antibiotics are not used for a] common cough or cold but something more serious like a chest infection or an ear infection.”

(P13; recruitment group 2, one child aged 15 months)

“When I was younger, it would just be if you’re not well or you’ve got a chest infection or something, you would get given antibiotics. But now you don’t get given them if you have a chest infection because the chest infection might not be bad enough for antibiotics.”

(P16; recruitment group 2, two children aged 6 months and 2 years old)

Lastly, there was a perceived need to complete antibiotic courses and take antibiotics as prescribed. Most attributed this advice to prevent relapse of infections. Other parents were less certain. A few parents attributed this advice to prevent antibiotic resistance.

“See that’s the other thing about taking [antibiotics] as they’re prescribed and missing a dose. I’m someone who always says ‘Oh make sure you finish the course’ and my husband is like ‘Oh no, it’s fine the symptoms have gone’, and I said ‘Yeah, well that’s not how it works, you have to make sure it’s all gone’.”

(P11; recruitment group 2, one child aged 20 months)

“I know they should be taken for seven days. [...] I wish I knew why, I used to know why and then I forgot. So when the child gets over the infection they should still be continued including the seventh day.”

(P5; recruitment group 2, three children aged 2, 4 and 7 years old)

Theme 4: Parents’ understanding of antibiotic resistance

4a. Description and knowledge of antibiotic resistance

Although parents had heard of the term, they had trepidations about explaining “antibiotic resistance”. Some parents understood that antibiotic resistance comes about when bacteria “learn to resist the effects of antibiotics” (Participant #3) or when bacteria mutate and resist the effects of a specific antibiotic. Other parents misunderstood antibiotic resistance as when a person does not respond to antibiotics or as the individual becoming resistant to antibiotics. A small number of parents could not recall what antibiotic resistance was, or had little personal knowledge about

antibiotic resistance. Parents' description and understanding of antibiotic resistance did not appear to be related to whether or not they attended their GP.

"If you use antibiotics too much then the antibiotics stop working on those infections because the little bugs get used to it and they get a little bit stronger and then they just don't work anymore."

(P16; recruitment group 2, two children aged 6 months and 2 years old)

"I'm guessing it's when the patient is not responding to the treatment or it's not having an effect, but I haven't really heard it before to be honest."

(P5; recruitment group 2, three children aged 2, 4 and 7 years old)

"We are slowly building a resistance to certain antibiotics because they are overused and overprescribed."

(P1; recruitment group 3, one child aged 10 months)

Parents' knowledge about antibiotic resistance came from media and internet search engines and less so from their healthcare provider.

"I've seen things, particularly on the BBC news. It seems to be fairly regularly they say 'this [infection] wasn't able to be treated by antibiotics'."

(P11; recruitment group 2, one child aged 20 months)

"Everybody would generally say the GP, I mean in the current NHS situation I don't think the GP can really have the time to explain this, so I wouldn't go to the GP. I would go to Google."

(P5; recruitment group 2, three children aged 2, 4 and 7 years old)

4b. Frequent antibiotic use and inappropriate behaviours contribute to antibiotic resistance

Parents who had heard of the term "antibiotic resistance" were quick to point out that antibiotic resistance occurs predominately because of using antibiotics inappropriately. This they understood to be because of antibiotic overuse, using antibiotics for inappropriate indications (e.g. viral infections) or not completing antibiotic courses.

“[Antibiotic resistance] is a problem with overuse of antibiotics, so the more we use them the more that the bacteria can build up a resistance against the antibiotics and that causes a massive problem.”

(P4; recruitment group 3, two children aged 19 months and 10 weeks)

“If antibiotics are taken for infections that aren’t bacterial, it could cause resistance.”

(P1; recruitment group 3, one child aged 10 months)

“If you don’t take the full [antibiotic] course, the surviving bacteria can then mutate and are then resistant, well they are resistant to the antibiotic you are taking.”

(P10 father; recruitment group 1, one child aged 16 months)

However, the majority of parents did not perceive a relationship between their individual consumption of antibiotics and the development of antibiotic resistance in the community.

“I would hope that because we try not to take [antibiotics] too often that perhaps [antibiotic resistance] wouldn’t affect us as much compared to somebody who took them as a matter of course every time somebody was poorly.”

(P11; recruitment group 2, one child aged 20 months)

Two parents thought that using household antibacterial products promotes antibiotic resistance.

One parent thought that antibiotics were not solely to blame for antibiotic resistance.

“All the anti-bacterial wipes that you see for everything, the cleaning products and all that, I mean certainly there is a time and a place for them but not as a kind of everyday thing.”

(P10 father; recruitment group 1, one child aged 16 months)

“[Sometimes antibiotic resistance occurs] because over time bacteria do mutate so they could just be a new strain that has appeared, not necessarily because of the antibiotics.”

(P1; recruitment group 3, one child aged 10 months)

Theme 5: Perceived consequences of antibiotic resistance

5a. Implications of antibiotic resistance for patients

Many parents realised that antibiotic resistance (or their understanding thereof) will make simple infections more severe because of resistant bacteria affecting the body’s natural immunity to cope

and that many patients will not be cured and could die. Those patients in hospitals were deemed at greatest risk of the effects of antibiotic resistance.

“[...] Catching infections that could become much more severe than they would have been previously. The body’s natural immunity might not be as effective as it would normally be. This will eventually cause problems if it continues, people won’t be able to treat simple infections, people will start dying.”

(P1; recruitment group 3, one child aged 10 months)

Some parents were aware that antibiotic-resistant infections would make recovery from infections longer and that people would “suffer”, putting certain population subgroups at risk of serious illness (e.g. chronic health problems, the young, elderly). However, other parents considered that although patients will be sicker initially, humans will overcome antibiotic resistance because of an adaptable immunity.

“I suppose vulnerable patients may well die from bugs or diseases which affect them. Patients who are elderly, patients who have multiple health problems, and I suppose the young as well, babies and infants, people who are vulnerable would probably suffer because they would be more at risk from diseases and bugs.”

(P20 father; recruitment group 1, one child aged 2 years old)

“In the long run we probably won’t be [sicker], maybe initially, but you’ve got a learned immunity. If you give your body a chance to fight [the infection] then maybe if you get it again you’ll be able to fight it more quickly, whereas if you’ve always relied on a drug to do the nitty gritty work for you, your immune system hasn’t had a chance to learn, and maybe that will be the way it works.”

(P2; recruitment group 1, three children child aged 3, 7, 9 years old)

5b. Impact of antibiotic resistance on close family

Parents had a sense of unrealistic optimism about how antibiotic resistance was likely to affect their family. Most parents perceived their own family at low risk of antibiotic resistance (or their interpretation thereof) because they considered themselves to be low-users of antibiotics or because they were less focussed on stringent hygiene measures.

"I would say we are relatively low risk. I'm of the school of let kids eat a bit of mud and don't blast everything with Dettol. I think it's important that you have your own little healthy microbiome that helps your immune system function as well as it can."

(P19; recruitment group 3, one child aged 3 years old)

"I guess some children probably have more illnesses, don't they? My friend's child has had a lot of infections, has been in hospital a lot and so I imagine that he's probably been prescribed more antibiotics than my children. So, I guess he would be developing more of a resistance than my children."

(P16; recruitment group 2, two children aged 6 months and 2 years old)

Very few parents were aware that resistant bacteria could be transferred between humans. One parent correctly identified that antibiotic resistance is a community problem because bacteria are transmissible.

"[The impact of antibiotic resistance] depends on what disease, the resistance is in the disease, not in the person, so actually, what you do as a society impacts each individual. It's the same with pollution, you can't say 'Oh well, we don't burn much fossil fuels in this house, so there's not going to be many [pollution] in our garden'. Just because you don't use antibiotics, it doesn't mean the bacteria that get into your body are going to be ones that aren't resistant because they're separate from you."

(P17; recruitment group 1, one child aged 6 months)

Others thought that the implication of antibiotic resistance, although a possibility, was a problem for the future and found it difficult to relate to.

"I'm not sure whether [antibiotic resistance will affect them]. As far as I understand, it's looking ahead so perhaps my daughter's generation or the generation afterwards, just thinking long term, that at some point there might be a bigger health crisis if there was a bug that couldn't be treated with antibiotics."

(P20 father; recruitment group 1, one child aged 2 years old)

"Because it's not real at the moment, you know, it's not affected me [...] I haven't seen it affect anyone that I know, and I think those sorts of things are still very abstract."

(P3; recruitment group 2, one children aged 2.5 years old)

Parents were divided as to the likely impact of antibiotic resistance on their immediate family compared to other families in the community. Some considered that antibiotic resistance would

likely affect everyone the same, whilst other parents perceived that antibiotic resistance would likely affect younger children more than the parents.

“I don't think [that antibiotic resistance will affect everybody]. I know that there are more health problems in different social demographics and that there is perhaps a bit of an inequality in people in a lower social demographic. They might have a shorter life expectancy. In terms of antibiotics, I wouldn't have thought it would make a difference as far as I know.”

(P20 father; recruitment group 1, one child aged 2 years old)

“I mean [my child is] much younger, if he's got an infection, antibiotic resistance would be a lot more serious for him than if I got it, I mean potentially life threatening, you know, for a two-year-old to get some kind of multi [dose] resistance nastiness.”

(P7; recruitment group 1; one child aged 21 months)

5c. Healthcare implications

Many parents recognised that antibiotic resistance would make future courses of antibiotics ineffective leaving fewer options, require more costly third and fourth-line antibiotics or further interventions to treat infection. However, other parents thought that society would simply have to explore different ways of trying to treat infections.

“[Antibiotic resistance] could just make life more difficult for [patients] in that if you've got an infection, you can only have antibiotics that are given through a [intravenous] drip, or a third or a fourth line antibiotic, which means you have to be in hospital for that; and it's a lot more expensive.”

(P7; recruitment group 1; one child aged 21 months)

Some parents recognised that antibiotic resistance presents a wider health problem. They recognised that antibiotic resistance might impact on health services e.g. increase appointment waiting times. Only a few recognised that resistant bacteria might affect routine hospital procedures.

“NHS services might be struggling more in future, and then if you need to get an appointment for yourself, then you may struggle.”

(P1; recruitment group 3, one child aged 10 months)

“Yes, going into hospital for anything routine, I’d be quite anxious of that.”

(P2; recruitment group 1, three children child aged 3, 7, 9 years old)

Theme 6: Ways to reduce antibiotic resistance in response to campaign materials

6a. Healthy lifestyle choices to reduce antibiotic resistance

Overall, parents presented themselves and their families as morally responsible i.e. trying to do the correct thing by following public health guidance and medical advice. They perceived that changing one’s lifestyle through healthy diet and exercise could reduce reliance on antibiotics. A few parents also discussed “boosting” their child’s immune system through vaccination programmes whilst others perceived using less household anti-bacterial products would reduce the changes of antibiotic resistance (see 4b Frequent antibiotic use and inappropriate behaviours contribute to antibiotic resistance).

“Encourage others to self-manage their own healthcare, and particularly through diet, [...] and also exercise [will reduce antibiotic resistance]. If people look after their bodies [...], I think [this] will reduce demand on NHS resources or feeling of entitlement for medication.”

(P6 father; recruitment group 3, one child aged 5 years old)

“Eat [better], eat less processed food. I suppose [antibiotic resistance] is happening because of what we put in our bodies, no? About the chemicals.”

(P5; recruitment group 2, three children aged 2, 4 and 7 years old)

6b. Prudent use of antibiotics

Parents thought that antibiotic resistance could be reduced by using antibiotics appropriately, completing antibiotic courses and conserving antibiotics for more severe infections. Parents were aware not to ask for antibiotics or share them. They perceived themselves as low users of antibiotics, often not able to recall the last time they had taken an antibiotic. Other parents were unsure as to how they could reduce antibiotic resistance themselves as it is part of a “much bigger” picture and that a collective public effort was needed to use fewer antibiotics.

“[There comes a point] when do you need [antibiotics], and save it for more severe cases for yourself.”

(P12; recruitment group 2, one child aged 2 years old)

“Don’t take [antibiotics] for things when you don’t need them.”

(P16; recruitment group 2, two children aged 6 months and 2 years old)

Theme 7: Parents’ reflections on current antibiotic awareness materials

7a. Perceived personal relevance of campaigns

None of the parents had seen examples of current public antibiotic awareness campaigns in the UK. Many parents were unaware of some of the key issues contributing to antibiotic resistance and that antibiotics were used beyond simply treating infections. They were surprised at the healthcare-related cost of antibiotic resistance and the number of people that die across Europe from infections resistant to antibiotics. Parents were unaware that only a very small percentage of sore throats for example, benefit from antibiotics.

“[The Antibiotic Guardian leaflet] tells a story and it tells you what to do and what not to do, so yeah. Shame it’s not in more places.”

(P19; recruitment group 3, one child aged 3 years old)

“Is that for [antibiotic resistance]? The reason [for antibiotic resistance] is from the overuse of antibiotics?”

(P5; recruitment group 2, three children aged 2, 4 and 7 years old)

7b. Perceptions of enablement of campaign messages

In response to campaign messages to reduce antibiotic consumption, most parents were happy to avoid antibiotics for simple “low level” symptoms they felt comfortable managing at home e.g. fever responding to paracetamol. However, many parents would consult for symptoms they were less comfortable with dealing at home e.g. earache, and this was dependent on the child’s symptoms and response to over-the-counter medication, symptom duration, perceived severity and the past experiences of parents managing these sorts of symptoms.

“Generally, a cough and a cold, I’d be happy with. Temperature that’s responding to Calpol I’m happy with, general lethargy isn’t a bad thing all the time. So yes, that sort of thing, so just kind of low level and even things like rashes.”

(P15; recruitment group 2, four children child aged 11 months, 6, 8, 10 years old)

“But if they’re crying with pain, like I was [referring to earache], [...] then it’s got to a point where it’s just a bit too much to handle.”

(P17; recruitment group 1, one child aged 6 months)

“I think earache is one of those, I don’t know why but I think I would almost always take them to the doctor straightaway. I think partly because it’s really uncomfortable and I know how uncomfortable it is. [...] But if it responds to Calpol or some kind of pain relief and it’s not getting progressively worse I think I probably wouldn’t go straightaway.”

(P15; recruitment group 2, four children child aged 11 months, 6, 8, 10 years old)

Some parents did not appreciate the “scaremongering” in the leaflets and preferred more practical information about what they personally can do to reduce antibiotic resistance.

“Don’t resort to scaremongering, even though it’s good to know the facts. I’m not saying that the facts are wrong, of course, but maybe present it in a less daunting way, and definitely connect it to what we can do and don’t just give a website. I’ve never seen this before, I’m actually laughing because I’ve never seen raising someone’s fear and then, oh, here’s a website.”

(P5; recruitment group 2, three children aged 2, 4 and 7 years old)

One parent recognised that there was an antithesis between public health messages that promote getting better without antibiotics, whilst other campaigns highlight that people may die without antibiotics.

“The problem is that there’s a mixed message. When it comes to like public health messages you’ve got, on the one hand that [for] the vast majority of infections, you can get well without antibiotics, you don’t need them, [and] you can get well on your own. And then, on the other hand, they’re saying that in the world in the future where we don’t have antibiotics, people might die. So, like how do you balance it? On the one hand, you’ve got a fear message and, on the other hand, you’ve got a positive message [...]. Both of those messages fight against each other. So if people think [they] can get well without antibiotics, why should [they] be worried about a world without antibiotics.”

(P8; recruitment group 3, one child aged 3 years old)

Theme 8: Social responsibility to inform parents about antibiotic resistance

8a. Better communication about antibiotics and resistance, and diagnostic tools during clinical consultations

Parents were aware that there is a drive for GPs to reduce antibiotic prescribing. They recognised that GPs were hard-pressed and often prescribed antibiotics just to be safe. However, they also urged clinicians to “stick to their guns” and that trust in the GP or nurse was needed to make the correct decision. A few parents wanted more transparent communication about different treatment strategies with a clear plan. One parent wanted clinicians to explain the reasons why antibiotics were prescribed (or not) including giving information about antibiotic resistance when antibiotics were going to be considered.

“I guess GPs and nurses need to stick to their guns more in terms of they don’t feel it’s necessary or maybe there’s a lack of education amongst health professionals about antibiotic resistance. So, it might be that [GPs] need more education and training so that they can reinforce that message to patients and parents and anyone else who is saying we want antibiotics when really they don’t need antibiotics.”

(P13; recruitment group 2, one child aged 15 months)

“...it would give me more confidence to have a discussion with a GP around knowing the facts about why [antibiotics] were being prescribed.”

(P4; recruitment group 3, two children aged 19 months and 10 weeks)

“...it’s all about the communication and the feeling of control and feeling that you can go back [to the GP].”

(P8; recruitment group 3, one child aged 3 years old)

One parent was aware that there was technology that could distinguish infections that needed antibiotics and wanted their clinician in the community to have better diagnostic tools but were aware that these needed further evaluation.

“Do you remember the machine that could decide whether it was viral or bacterial? [...] and then they would say, oh, antibiotics is definitely needed here or not. So I thought that was amazing and that every GP practice should have one tomorrow, but then if it’s not that accurate then maybe it’s not the answer.”

(P4; recruitment group 3, two children aged 19 months and 10 weeks)

8b. Better public campaign strategies on antibiotic resistance in terms of content, timing, and targeting populations

Parents suggested that future campaigns should target people about antibiotic stewardship in a context outside illness, using a simple universal message “directed” at individuals and families. They recognised that changing a mind-set about the benefits of antibiotics might take a generation, and that a bigger “One Health” approach was needed to tackle antibiotic use in animals.

“It’s the little things as much as the big things. So, for me, using drugs appropriately is a big thing, but maybe more about what you can do in everyday life, because I don’t know if there are things that you can do that I don’t do and it hasn’t occurred to me. Honestly, it’s never occurred to me to think about it properly before now in a context outside illness.”

(P19; recruitment group 3, one child aged 3 years old)

“Aim it more at the patient and their family, and say what implications it could have for them directly in future. [...] Because you tend to read things like this [leaflet] and easily forget it, whereas if you realise it may have problems for your children in future for example, then you do start to worry a bit more, and it is something you remember.”

(P1; recruitment group 3, one child aged 10 months)

They also wanted information about when antibiotics were likely to be needed for common childhood infections and the chances of speeding up recovery.

“If there was something that said antibiotics can help you get better in five days but you could get better yourself without taking them in seven days, you might go, oh okay, that might be something that we could try.”

(P18; recruitment group 3, four children aged 11 months, 6, 8, 10 years old)

“I think you learn as a parent over time what kind of ill is normal ill and what’s not. Perhaps it would be useful to know what things really don’t need antibiotics and then you’ll be more confident with the fact you can give Calpol and you don’t need to go to the doctor.”

(P20 father; recruitment group 1, one child aged 2 years old)

Interestingly, one parent suggested refocussing campaign messages by moving away from a negative inculpatory tone to a positive one by building up a child's immune system with fewer antibiotics.

“And if we saw getting sick as a milestone, not serious sickness, but mild viral illness and even mild bacterial illnesses, [...] if we saw it as a milestone, as a thing that our bodies can do, we are naturally equipped [...]. So, a vaccine is [...] like a training program for your immune system, whereas an antibiotic is not helping your immune system develop, other than just it's getting rid of the thing that your immune system is also fighting. So, I wonder whether messages around just how great your immune [system is] and how you could make your child be the best your child can be, would be more helpful.”

(P8; recruitment group 3, one child aged 3 years old)

Although many parents suggested TV adverts, websites and social media might be good for disseminating new information about antibiotic resistance, some parents said that this did not fit into their busy, everyday lives. They proposed other avenues like face-face dissemination at playgroups and charities e.g. NCTs (National Childbirth Trust) and other health contact opportunities e.g. health visitor.

“I think it's really important and whether that's in the form of access to healthcare or a leaflet. We [received] so much information when you first have a baby, any baby, even the fourth. I don't know if that's [already] included but I think it would be useful to give that information really.”

(P15; recruitment group 2, four children child aged 11 months, 6, 8, 10 years old)

6.5 Discussion

6.5.1 Summary of main findings

Parents had a sense of unrealistic optimism about how antibiotic resistance was likely to affect their family. They considered their families to be at low risk of antibiotic resistance because their families were “low users” of antibiotics. They did not perceive any association between their consumption of antibiotics and the development and spread of antibiotic-resistant bacteria in the community. Most parents thought they acted morally responsible and were quite reticent about

antibiotics for their children. Very few parents considered antibiotic resistance as a possible harm of antibiotics.

Parents wanted better communication from their clinician about different treatment strategies, why antibiotics were prescribed and about the potential impact of antibiotic resistance relevant to their families. Parents wanted future antibiotic awareness campaigns to have a universal message relevant to their families that fits into their daily lives. Campaigns should address when antibiotics are likely to be needed for common childhood infections and the chances of speeding up recovery with antibiotic treatment.

6.5.2 Strengths and limitations

6.5.2.1. Strengths

This study is one of only a handful of studies focussing on parents' concerns about taking antibiotics and antibiotic resistance and starts to address one of the five strategic objectives set out by the World Health Organization's Global Action Plan on Antimicrobial Resistance.(103, 104) I focussed on parents with preschool children as opposed to older children because (a) this subgroup has the highest unnecessary antibiotic prescribing in primary care; (b) this is a time where most parents feel their young child is most vulnerable (5); and (c) where the harmful effects of antibiotics on the human microbiome are likely to have the greatest impact.(105, 106)

Parents were sought through several recruitment strategies across different localities and from three parent groups based on their health-seeking behaviour, and whether or not an antibiotic was prescribed. Around a fifth of parents I interviewed were from non-British backgrounds bringing other expectations of health systems.

To ensure rigour, my strategy was systematic and I used a self-conscious approach to the research design, data collection, interpretation and communication. I was acutely aware that during the study, there were a number of media reports in the UK about national sepsis campaigns and child

deaths associated with life-threatening infections (e.g. meningitis) and incorporated this into the interview guide where possible. Assessing this study's dependability, I took this ever-changing context into account when interpreting the findings. This however, did not seem to have unduly influenced parents' perceptions about the role of antibiotics or downplayed the risks of antibiotics and antibiotic resistance.

I took steps to compare and contrast coding of some initial transcripts, refine the coding strategy and develop the thematic framework with my supervisor (STC). I have produced a detailed description of the methods employed to increase the study's dependability should this research be repeated in the future, albeit without the expectations of achieving similar results. This clear exposition of the process of data collection and analysis also allows the reader to judge whether the interpretation proffered is supported by the data.

I found that listening to interview recordings whilst reading the transcripts was a valuable exercise when it came to interpreting participants' intended meanings, by minimising the risk of coding de-contextualised transcripts inappropriately.

To ensure trustworthiness, I made concerted efforts to confirm that the reported findings were grounded in the data, rather than my pre-conceived ideas and biases by taking a reflexive approach. Triangulating my data collection, analysis and findings with an experienced supervising researcher (STC) to check and provide balance of my coding and thematic framework, enhanced its credibility and my reflexive approach.

6.5.2.2. Limitations

Methodologically, there is an accepted limitation of interview methods where there is potential for participants to filter what they disclose to the researcher by giving socially desirable answers.(107) This is potential enhanced where parents are being interviewed by a medical practitioner. However, parents were reassured there were no right or wrong answers to questions

and from interview data, parents were happy to speak freely about negatives experiences of healthcare and/or when they were unsure about their own knowledge.

I was particularly mindful of how I was interpreting what parents were saying. I adopted some useful communication tactics for improving the credibility of my findings by checking parents' understanding of what was expressed in the interviews and often confirmed that I had understood their comments by paraphrasing what had been said and repeating back my interpretations.

There was potential for recall bias where some parents had differing lengths of recall in relation to their child's infection and time of interview.(108) However, this risk was low because to be included in the study, parents had to recall a specific RTI illness episode within the last three months, and most parents were able to recall their child's illness experience in detail as evidenced from the interview data. That said, interviews can only provide insight into parents' perspectives on events not a direct window to the event itself (e.g. illness episode or GP consultation).(32)

Generalising from qualitative research is not appropriate as findings are bound to specific people, times and settings. In terms of transferability, the sampling and recruitment of parents was one of the main limitations of the study, as the sample was heavily biased towards middle-aged mothers. Although parents came across as well educated and were aware of the term "antibiotic resistance", they showed relatively limited understanding of antibiotic resistance or its implications. For those that were more knowledgeable about antibiotic resistance, there was little depth of their understanding of antibiotic resistance and its potential impact in the context of their families.

Despite concerted efforts to actively recruit from toddler groups and GP practices in more deprived areas, there was a lack of parents from deprived backgrounds, fathers and parents under the age of 25 years old. This study was limited to the greater Thames Valley region and therefore other opinions may be uncovered if repeated in other parts of the UK.

I tried to recruit parents purposively for a maximum variation sample. However, for pragmatic reasons, there was a degree of opportunistic sampling which might have introduced bias by

attracting certain types of parents: those who are naturally interested in research or those who had the time to participate. There is a chance therefore that these factors would influence any parent's likelihood of agreeing to participate.

6.5.3 Conclusions

Chapter 6 demonstrates that most parents are unperturbed that antibiotic resistance can affect their families. Parents did not link their families' consumption of antibiotics to the development and spread of antibiotic-resistant bacteria in the community. However, chapter 5 showed that children exposed to as low as two antibiotic courses in the previous year were more likely to have a subsequent RTI that did not respond to antibiotic treatment – a proportion of which may be related to an antibiotic-resistant infection as outlined in chapter 4.

To facilitate strategies parents would find acceptable to minimise antibiotic resistance for their children, better evidence on patient outcomes is needed for those children using fewer antibiotics on an individual (or household) basis, and marrying these findings to antibiotic resistance. The next chapter considers this and other implications for further research and clinical practice, both from this chapter and the preceding chapters in this thesis.

6.6 References

1. Hippisley-Cox J, Vinogradova Y. Q research. Trends in consultation rates in general practice 1995/1996 to 2008/2009: Analysis of the QResearch1 database. Final Report to the NHS Information Centre and Department of Health, Nottingham. NHS The Information Centre for Health and Social Care, University of Nottingham; 2009.
2. Sands R, Shanmugavadivel D, Stephenson T, Wood D. Medical problems presenting to paediatric emergency departments: 10 years on. *Emergency medicine journal* : EMJ. 2012;29(5):379-82.
3. Kai J. What worries parents when their preschool children are acutely ill, and why: a qualitative study. *BMJ (Clinical research ed)*. 1996;313(7063):983-6.
4. Neill SJ, Jones CH, Lakhanpaul M, Roland DT, Thompson MJ. Parents' help-seeking behaviours during acute childhood illness at home: A contribution to explanatory theory. *Journal of child health care : for professionals working with children in the hospital and community*. 2016;20(1):77-86.
5. Cabral C, Lucas PJ, Ingram J, Hay AD, Horwood J. "It's safer to ..." parent consulting and clinician antibiotic prescribing decisions for children with respiratory tract infections: An analysis across four qualitative studies. *Social science & medicine (1982)*. 2015;136-137:156-64.

6. de Bont EG, Loonen N, Hendrix DA, Lepot JM, Dinant GJ, Cals JW. Childhood fever: a qualitative study on parents' expectations and experiences during general practice out-of-hours care consultations. *BMC family practice*. 2015;16:131.
7. Ingram J, Cabral C, Hay AD, Lucas PJ, Horwood J. Parents' information needs, self-efficacy and influences on consulting for childhood respiratory tract infections: a qualitative study. *BMC family practice*. 2013;14:106.
8. Saunders NR, Tennis O, Jacobson S, Gans M, Dick PT. Parents' responses to symptoms of respiratory tract infection in their children. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2003;168(1):25-30.
9. Sharma M, Usherwood T. Up close - reasons why parents attend their general practitioner when their child is sick. *Australian family physician*. 2014;43(4):223-6.
10. de la Poza Abad M, Mas Dalmau G, Moreno Bakedano M, Gonzalez Gonzalez AI, Canellas Criado Y, Hernandez Anadon S, et al. Prescription Strategies in Acute Uncomplicated Respiratory Infections: A Randomized Clinical Trial. *JAMA internal medicine*. 2016;176(1):21-9.
11. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotics for respiratory infections. *The Cochrane database of systematic reviews*. 2013(4):Cd004417.
12. Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, et al. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. *BMJ (Clinical research ed)*. 2014;348:g1606.
13. Panagakou SG, Spyridis N, Papaevangelou V, Theodoridou KM, Goutziana GP, Theodoridou MN, et al. Antibiotic use for upper respiratory tract infections in children: a cross-sectional survey of knowledge, attitudes, and practices (KAP) of parents in Greece. *BMC pediatrics*. 2011;11:60.
14. Shlomo V, Adi R, Eliezer K. The knowledge and expectations of parents about the role of antibiotic treatment in upper respiratory tract infection--a survey among parents attending the primary physician with their sick child. *BMC family practice*. 2003;4:20.
15. Cantarero-Arevalo L, Hallas MP, Kaae S. Parental knowledge of antibiotic use in children with respiratory infections: a systematic review. *The International journal of pharmacy practice*. 2017;25(1):31-49.
16. Palmer DA, Bauchner H. Parents' and physicians' views on antibiotics. *Pediatrics*. 1997;99(6):E6.
17. Finkelstein JA, Stille CJ, Rifas-Shiman SL, Goldmann D. Watchful waiting for acute otitis media: are parents and physicians ready? *Pediatrics*. 2005;115(6):1466-73.
18. Tahtinen PA, Boonacker CW, Rovers MM, Schilder AG, Huovinen P, Liuksila PR, et al. Parental experiences and attitudes regarding the management of acute otitis media--a comparative questionnaire between Finland and The Netherlands. *Family practice*. 2009;26(6):488-92.
19. Kautz-Freimuth S, Redaelli M, Samel C, Civello D, Altin SV, Stock S. Parental views on acute otitis media (AOM) and its therapy in children--results of an exploratory survey in German childcare facilities. *BMC pediatrics*. 2015;15:199.
20. Trepka MJ, Belongia EA, Chyou PH, Davis JP, Schwartz B. The effect of a community intervention trial on parental knowledge and awareness of antibiotic resistance and appropriate antibiotic use in children. *Pediatrics*. 2001;107(1):E6.
21. Coxeter PD, Mar CD, Hoffmann TC. Parents' Expectations and Experiences of Antibiotics for Acute Respiratory Infections in Primary Care. *Annals of family medicine*. 2017;15(2):149-54.
22. McNulty CAM, Boyle P, Nichols T, Clappison P, Davey P. Don't wear me out--the public's knowledge of and attitudes to antibiotic use. *Journal of Antimicrobial Chemotherapy*. 2007;59(4):727-38.
23. Stuppelle-Harris L. Public views on antimicrobial resistance. London: Sciencewise; 2014.
24. Finkelstein JA, Dutta-Linn M, Meyer R, Goldman R. Childhood infections, antibiotics, and resistance: what are parents saying now? *Clinical pediatrics*. 2014;53(2):145-50.
25. Wun YT, Lam TP, Lam KF, Sun KS. Antibiotic use: do parents act differently for their children? *International journal of clinical practice*. 2012;66(12):1197-203.

26. Barden LS, Dowell SF, Schwartz B, Lackey C. Current attitudes regarding use of antimicrobial agents: results from physician's and parents' focus group discussions. *Clinical pediatrics*. 1998;37(11):665-71.
27. Jonsson H, Haraldsson RH. Parents' perspectives on otitis media and antibiotics. A qualitative study. *Scandinavian journal of primary health care*. 2002;20(1):35-9.
28. McCullough AR, Parekh S, Rathbone J, Del Mar CB, Hoffmann TC. A systematic review of the public's knowledge and beliefs about antibiotic resistance. *The Journal of antimicrobial chemotherapy*. 2016;71(1):27-33.
29. Szymczak JE, Klieger SB, Miller M, Fiks AG, Gerber JS. What Parents Think About the Risks and Benefits of Antibiotics for Their Child's Acute Respiratory Tract Infection. *Journal of the Pediatric Infectious Diseases Society*. 2017.
30. Cabral C, Ingram J, Lucas PJ, Redmond NM, Kai J, Hay AD, et al. Influence of Clinical Communication on Parents' Antibiotic Expectations for Children With Respiratory Tract Infections. *Annals of family medicine*. 2016;14(2):141-7.
31. HealthtalkOnline. Flu or Flu-like illness in chronically ill or disabled children 2014 [Available from: <http://www.healthtalk.org/peoples-experiences/pregnancy-children/flu-or-flu-illness-chronically-ill-or-disabled-children/parents-concerns-about-taking-antibiotics>].
32. Halls A, van't Hoff C, Little P, Verheij T, Leydon GM. Qualitative interview study of parents' perspectives, concerns and experiences of the management of lower respiratory tract infections in children in primary care. *BMJ open*. 2017;7(9).
33. Ashiru-Oredope D, Hopkins S. Antimicrobial stewardship: English Surveillance Programme for Antimicrobial Utilization and Resistance (ESPAUR). *The Journal of antimicrobial chemotherapy*. 2013;68(11):2421-3.
34. Charani E, Edwards R, Sevdalis N, Alexandrou B, Sibley E, Mullett D, et al. Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2011;53(7):651-62.
35. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *The Cochrane database of systematic reviews*. 2017;2:Cd003543.
36. Davey P, Peden C, Charani E, Marwick C, Michie S. Time for action-Improving the design and reporting of behaviour change interventions for antimicrobial stewardship in hospitals: Early findings from a systematic review. *International journal of antimicrobial agents*. 2015;45(3):203-12.
37. Ranji SR, Steinman MA, Shojania KG, Gonzales R. Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis. *Medical care*. 2008;46(8):847-62.
38. Tonkin-Crine SK, Tan PS, van Hecke O, Wang K, Roberts NW, McCullough A, et al. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. *The Cochrane database of systematic reviews*. 2017;9:Cd012252.
39. French SD, Green SE, O'Connor DA, McKenzie JE, Francis JJ, Michie S, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. *Implementation science : IS*. 2012;7:38.
40. Bandura A. *Social Foundations of Thought & Action: A Social Cognitive Theory*. Englewood Cliffs, N.J: Prentice Hall; 1986.
41. Michie S. Designing and implementing behaviour change interventions to improve population health. *Journal of health services research & policy*. 2008;13 Suppl 3:64-9.
42. McNulty CA, Francis NA. Optimizing antibiotic prescribing in primary care settings in the UK: findings of a BSAC multi-disciplinary workshop 2009. *The Journal of antimicrobial chemotherapy*. 2010;65(11):2278-84.
43. Edgar T, Boyd SD, Palame MJ. Sustainability for behaviour change in the fight against antibiotic resistance: a social marketing framework. *The Journal of antimicrobial chemotherapy*. 2009;63(2):230-7.

44. Stead M, Gordon R, Angus K, McDermott L. A Systematic Review of Social Marketing Effectiveness Health Education. 2007;107:126-91.
45. Stalsby Lundborg C, Tamhankar AJ. Understanding and changing human behaviour--antibiotic mainstreaming as an approach to facilitate modification of provider and consumer behaviour. *Upsala journal of medical sciences*. 2014;119(2):125-33.
46. Leventhal H, Leventhal EA, Contrada RJ. Self-regulation, health, and behavior: A perceptual-cognitive approach. *Psychology & Health*. 1998;13(4):717-33.
47. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with *E. coli* UTIs. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2006;56(530):686-92.
48. McNulty CA, Richards J, Livermore DM, Little P, Charlett A, Freeman E, et al. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *The Journal of antimicrobial chemotherapy*. 2006;58(5):1000-8.
49. Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. *Lancet (London, England)*. 2016;387(10029):1743-52.
50. Tonkin-Crine S, Anthierens S, Francis NA, Brugman C, Fernandez-Vandellos P, Krawczyk J, et al. Exploring patients' views of primary care consultations with contrasting interventions for acute cough: a six-country European qualitative study. *NPJ primary care respiratory medicine*. 2014;24:14026.
51. Blair PS, Turnbull S, Ingram J, Redmond N, Lucas PJ, Cabral C, et al. Feasibility cluster randomised controlled trial of a within-consultation intervention to reduce antibiotic prescribing for children presenting to primary care with acute respiratory tract infection and cough. *BMJ open*. 2017;7(5):e014506.
52. de Bont EG, Dinant GJ, Elshout G, van Well G, Francis NA, Winkens B, et al. An illness-focused interactive booklet to optimise management and medication for childhood fever and infections in out-of-hours primary care: study protocol for a cluster randomised trial. *Trials*. 2016;17(1):547.
53. Little P, Stuart B, Francis N, Douglas E, Tonkin-Crine S, Anthierens S, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet (London, England)*. 2013;382(9899):1175-82.
54. van der Velden AW, Kuyvenhoven MM, Verheij TJM. Improving antibiotic prescribing quality by an intervention embedded in the primary care practice accreditation: the ARTI4 randomized trial. *Journal of Antimicrobial Chemotherapy*. 2016;71(1):257-63.
55. Meeker D, Linder JA, Fox CR, Friedberg MW, Persell SD, Goldstein NJ, et al. Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices: A Randomized Clinical Trial. *Jama*. 2016;315(6):562-70.
56. Llor C, Cots JM, Hernández S, Ortega J, Arranz J, Monedero MJ, et al. Effectiveness of two types of intervention on antibiotic prescribing in respiratory tract infections in Primary Care in Spain. *Happy Audit Study. Atención Primaria*. 2014;46(9):492-500.
57. Cabral C, Ingram J, Hay AD, Horwood J. "They just say everything's a virus"--parent's judgment of the credibility of clinician communication in primary care consultations for respiratory tract infections in children: a qualitative study. *Patient education and counseling*. 2014;95(2):248-53.
58. Horwood J, Cabral C, Hay AD, Ingram J. Primary care clinician antibiotic prescribing decisions in consultations for children with RTIs: a qualitative interview study. *British Journal of General Practice*. 2016;66(644):e207-e13.
59. Redmond NM, Davies R, Christensen H, Blair PS, Lovering AM, Leeming JP, et al. The TARGET cohort study protocol: a prospective primary care cohort study to derive and validate a clinical prediction rule to improve the targeting of antibiotics in children with respiratory tract illnesses. *BMC health services research*. 2013;13:322.
60. Hay AD, Redmond NM, Turnbull S, Christensen H, Thornton H, Little P, et al. Development and internal validation of a clinical rule to improve antibiotic use in children

presenting to primary care with acute respiratory tract infection and cough: a prognostic cohort study. *The Lancet Respiratory Medicine*. 2016;4(11):902-10.

61. Pinder RJ, Berry D, Sallis A, Chadborn T. Antibiotic prescribing and behaviour change in healthcare settings: literature review and behavioural analysis. Department of Health & Public Health England; 2015.
62. Mishler EG. Research interviewing: Context and narrative: Harvard University Press; 1991.
63. Sandelowski M. Telling stories: narrative approaches in qualitative research. *Image--the journal of nursing scholarship*. 1991;23(3):161-6.
64. Patton MQ. Qualitative research and evaluation methods. 3rd ed. Thousand Oaks, CA: Sage; 2002.
65. Braun V, Clarke V. Interactive data collection 1: interviews. London: Sage Publications Ltd; 2013. 77-106 p.
66. Palys T. Purposive sampling. In: Given M, editor. *The Sage Encyclopedia of Qualitative Research Methods 2*. Los Angeles: Sage; 2008. p. 697-8.
67. Cresswell JW, Plano Clark VL. Designing and conducting mixed method research. 2nd ed. Thousand Oaks, CA: Sage; 2011.
68. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Administration and policy in mental health*. 2015;42(5):533-44.
69. Bernard HR. Research methods in anthropology: Qualitative and quantitative approaches. 3rd ed. Walnut Creek, CA: Alta Mira Press; 2002.
70. Marshall MN. Sampling for qualitative research. *Family practice*. 1996;13(6):522-8.
71. Sandelowski M. Sample size in qualitative research. *Research in Nursing & Health*. 1995;18:179-83.
72. Vogt WP. Dictionary of Statistics and Methodology: A Nontechnical Guide for the Social Sciences. London: Sage; 1999.
73. Braun V, Clarke V. Planning and designing qualitative research. *Successful Qualitative Research: a practical guide for beginners* London: Sage Publications Ltd; 2013. p. 77-106.
74. Brooks L, Shaw A, Sharp D, Hay AD. Towards a better understanding of patients' perspectives of antibiotic resistance and MRSA: a qualitative study. *Family practice*. 2008;25(5):341-8.
75. Morse JM. The significance of saturation. *Qualitative Health Research*. 1995(10):3-5.
76. Fusch PI, Ness LR. Are We There Yet? Data Saturation in Qualitative Research. *Qualitative Report*. 2015;20(9):1408-16.
77. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field Methods*. 2006;18(1):59-82.
78. Corbin J, Strauss A. Theoretical Sampling. *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory*. London: SAGE; 2015. p. 134-51.
79. Malterud K. Qualitative research: standards, challenges, and guidelines. *Lancet (London, England)*. 2001;358(9280):483-8.
80. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res*. 2015.
81. Hamberg K, Johansson E, Lindgren G, Westman G. Scientific rigour in qualitative research--examples from a study of women's health in family practice. *Family practice*. 1994;11(2):176-81.
82. Morse JM, Field PA. Nursing research: The application of qualitative approaches. 2nd ed. Cheltenham: Nelson Thames; 2002.
83. Mason M. Sample Size and Saturation in PhD Studies Using Qualitative Interviews. 2010. 2010;11(3).
84. Hansen MP, Howlett J, Del Mar C, Hoffmann TC. Parents' beliefs and knowledge about the management of acute otitis media: a qualitative study. *BMC family practice*. 2015;16:82.
85. Chew-Graham CA, May CR, Perry MS. Qualitative research and the problem of judgement: lessons from interviewing fellow professionals. *Family practice*. 2002;19(3):285-9.

86. Berger R. Now I see it, now I don't: researcher's position and reflexivity in qualitative research. *Qualitative Research*. 2015;15(2):219-34.
87. Bernard HR. *Social research methods: Qualitative and quantitative approaches*. 2nd ed. Thousand Oaks, CA: Sage; 2012.
88. Britten N, Jones R, Murphy E, Stacy R. Qualitative research methods in general practice and primary care. *Family practice*. 1995;12(1):104-14.
89. Hoddinott P, Pill R. Qualitative research interviewing by general practitioners. A personal view of the opportunities and pitfalls. *Family practice*. 1997;14(4):307-12.
90. Bernard HR. *Research methods in anthropology: Qualitative and quantitative approaches*. 4 ed. Lanham, MD: AltaMira Press 2006.
91. Braun V, Clarke V. Using Thematic Analysis in Psychology. *Qualitative Research in Psychology*. 2006;3:77-101.
92. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman B, Burgess R, editors. *Analyzing qualitative data*. London and New York: Routledge; 1994. p. 173–94.
93. Ritchie J, J L, McNaughton Nicholls C, Ormston R. *Analysis: Principles and Processes*. Qualitative Research Practice London: Sage; 2014.
94. Glaser BG, Strauss AL. *The Discovery of Grounded Theory: Strategies for Qualitative Research*. New York, NY: AldineDe Gruyter; 1967.
95. Barbour RS. Checklists for improving rigour in qualitative research: a case of the tail wagging the dog? *BMJ (Clinical research ed)*. 2001;322(7294):1115-7.
96. Ziebland S, McPherson A. Making sense of qualitative data analysis: an introduction with illustrations from DIPEX (personal experiences of health and illness). *Medical education*. 2006;40(5):405-14.
97. Dixon-Woods M, Shaw RL, Agarwal S, Smith JA. The problem of appraising qualitative research. *Quality & safety in health care*. 2004;13(3):223-5.
98. Mays N, Pope C. Qualitative research in health care. Assessing quality in qualitative research. *BMJ (Clinical research ed)*. 2000;320(7226):50-2.
99. Spencer L, Ritchie J, Lewis J, Dillon L. *Quality in qualitative evaluation: a framework for assessing research evidence*. Government Chief Social Researcher's Office; 2003.
100. Hannes K. Critical appraisal of qualitative research. In: Noyes J BA, Hannes K, Harden A, Harris J, Lewin S, Lockwood C., editor. *Supplementary Guidance for Inclusion of Qualitative Research in Cochrane Systematic Reviews of Interventions version 1 (updated August 2011)* Cochrane Collaboration Qualitative Methods Group, 2011.
101. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Academic medicine : journal of the Association of American Medical Colleges*. 2014;89(9):1245-51.
102. Tavare A, O'Flynn N. Recognition, diagnosis, and early management of sepsis: NICE guideline. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2017;67(657):185-6.
103. World Health Organisation. *Antimicrobial resistance: global report on surveillance*. 2014 April 2014.
104. World Health Organization. *Global Action Plan On Antimicrobial Resistance*. 2015.
105. Bosch AA, de Steenhuijsen Piters WA, van Houten MA, Chu M, Biesbroek G, Kool J, et al. Maturation of the Infant Respiratory Microbiota, Environmental Drivers and Health Consequences: A Prospective Cohort Study. *American journal of respiratory and critical care medicine*. 2017.
106. Turta O, Rautava S. Antibiotics, obesity and the link to microbes - what are we doing to our children? *BMC Medicine*. 2016;14:57.
107. Carroll FE, Rooshenas L, Owen-Smith A, Al-Janabi H, Hollinghurst S, Hay AD. Factors influencing parents' decision-making when sending children with respiratory tract infections to nursery. *Journal of public health (Oxford, England)*. 2016;38(2):281-8.
108. King N, Horrocks C. *Interviews in Qualitative Research*. London: SAGE; 2010.

Chapter 7 Discussion

7.1 Summary of main findings

- For common infections in the community, patients with laboratory confirmed antibiotic-resistant *E. coli* urinary tract infections (UTI) or *S. pneumoniae* respiratory tract infections (RTI) are more likely to experience worse clinical outcomes than patients whose infections are antibiotic-sensitive.
- In a nationally representative random sample of acute RTI consultations in preschool children (2009 -2016), children prescribed two or more antibiotic courses in the previous year for acute RTI had greater likelihood of antibiotic “response failure” to treatment for subsequent acute RTIs compared to children that had received no previous antibiotics.
- When accounting for multiple individual RTI episodes presenting in each child nested within each general practice, secondary analysis supported the findings from the primary analysis above.
- Qualitative interviews revealed that parents of preschool children had a sense of unrealistic optimism about how antibiotic resistance is likely to affect their family. They thought their families were at low risk of antibiotic resistance because their families were “low users” of antibiotics and did not perceive an association between their individual consumption of antibiotics and the development and spread of antibiotic-resistant bacteria in the community.
- Although most parents were quite reticent about antibiotics for their children, very few considered antibiotic resistance as a possible harm of antibiotics. Parents wanted better communication from their clinician about different treatment strategies and why antibiotics were prescribed. In response to campaign materials, they wanted future antibiotic awareness campaigns to have a universal message about the potential impact of antibiotic resistance relevant to their families that slots into their daily lives.

7.2 Comparison with existing literature

7.2.1 The impact of antibiotic resistance on patient recovery from common infections in the community

Based on a systematic review of current best evidence, Chapter 4 found that antibiotic resistance has worse implications for patients with common and uncomplicated infections in the community, and may also impact on workload in primary care. The best evidence for this impact on patient illness burden is for antibiotic-resistant *E. coli* urinary tract infections (UTI) where patients were also more likely to re-consult a health care professional and experience prolonged and more severe symptoms than patients with antibiotic-sensitive infections.

Previous systematic reviews have demonstrated a clear association between commonly prescribed antibiotics in the community, and carriage of antibiotic-resistant bacteria.(1-3) These estimates are consistent with estimates of clinical response failure rates in community populations: for UTIs (14-38%)(4, 5); community-acquired pneumonia (11-24%)(6); and acute otitis media (7-24%).(7, 8) However, unlike the findings in Chapter 4, these earlier studies did not relate the specific contribution (or association) of antibiotic resistance to clinical outcomes.

Data on re-consultation rates were only available for *E. coli* UTIs and not on other types of infection. The estimates in Chapter 4 are comparable with other studies, 28% (357/1,283) vs 26-55%, (9, 10), and provide further insight into the impact that antibiotic resistance is likely to have on primary care workload, and increased health care costs.

Given that at least 1 in 3 women will experience a UTI during their lifetime (11), and that the incidence of UTIs is around 0.5 to 0.7 per person-year (12), the findings in Chapter 4 show that antibiotic resistance significantly impacts on patients' illness burden. This impact however may be much greater where the prevalence of antibiotic-resistant *E. coli* is higher e.g. in children with UTIs.(2) Recent evidence reports that the global pooled prevalence of trimethoprim resistance used as first-line antibiotic treatment for *E. coli* UTI in children is 23·6% (17·9-30·3%).(2) For

more common illnesses like RTIs, the impact of antibiotic-resistant *S. pneumoniae* CAP in adults may be considerable, as estimates vary considerably across European countries where around 1 to 50% of *S. pneumoniae* isolates have been recorded as non-susceptible to penicillin or macrolides.(13, 14)

The prevalence of resistant *E. coli* in the UTI studies included for clinical response failure (10·4%, 357/3,428) falls within the lower end of the spectrum compared to most community-based population estimates (5-53%) as this depends on the antibiotic susceptibility measured, the clinical criteria used for obtaining urine samples and diagnosing UTIs (15-18), and study population characteristics.(2) However, when examining resistance to the same antibiotic in community populations, our estimated prevalence of *E. coli* resistant to nitrofurantoin (1·8%, 3/171) for example, is similar to other studies (<2%).(16, 17) Similarly, the prevalence of resistant *S. pneumoniae* in CAP and AOM in our included studies are lower than population estimates (5·4%, (246/4,591) vs 8-33% for CAP (19, 20); 0·4% (353/3,407) vs 1-48% for AOM).(21, 22)

7.2.2 The relationship between antibiotic exposure and clinical response failure in preschool children with acute respiratory tract infections

Based on routinely collected primary care data, Chapter 5 demonstrated that 1% of preschool children with an acute respiratory tract infection (RTI) failed to respond to antibiotic treatment within 14 days of consulting in primary care. Referrals to a specialist service in secondary care within 14 days accounted for around half of response failures. This contrasts with previous population-based studies in the UK showing that around 1 in 10 patients of all ages prescribed antibiotics for an “acute RTI” (upper -, lower respiratory tract infection, acute otitis media) in the community experience an antibiotic ‘treatment failure’.(23, 24) Here, close to 95% of these antibiotic “treatment failures” were in the form of re-consultation and receipt of a different antibiotic prescription within 30 days of their initial prescription.

These former studies (23, 24) showed that the highest failure rates were for lower respiratory tract infections, which is comparable to the findings of Chapter 5. However, these studies did not determine “treatment failure rates” for younger children. One study in the USA examining failure rates in children aged 3 months to 12 years with acute otitis media, found that 10% required an additional antibiotic within 2–18 days over the 12 year study period.(25) The highest treatment failure rates were found in children under 2 years of age (15-18%). However, this study was based on inpatient, outpatient, and prescription drug claims in the USA and included injectable or intravenous antibiotics, which does not reflect routine primary care clinical practice in the UK.

These differences, however, can be explained by differences in definitions of antibiotic response failure. The definition used in Chapter 5 was developed to specifically reflect paediatric, rather than adult, consultations for acute RTIs in primary care: parents of young children tend to consult within a short period of time if their child’s symptoms are not improving and clinicians are inclined to get an early second opinion from specialist colleagues in secondary care. This is supported by evidence from a recent UK study of over 8,000 children with acute RTIs and cough where nearly a third of children consulted within 3 days of symptoms onset. Of children admitted to hospital, 75% were admitted within the first 14 days (62% between days 2 and 7).(26) This is supported by previous qualitative research (27), and findings from Chapter 6 that found that parents consult because of uncertainty about their child's illness rather than because they believe their child has a serious health problem and that clinicians, when uncertain about a young child’s diagnosis, would err on the side of caution.

Chapter 5 also observed that boys were more likely to have “response failure” than girls. This ties in with prospective evidence (26) and supporting theory where the impact of sex hormones on the T-helper 1/T-helper 2 cytokine balance has been proposed to explain the higher severity of most infectious diseases in males, especially for common paediatric viral infections.(28, 29)

Importantly, the underlying reasons for why antibiotic response failure events occur are multifactorial. Possible explanations include that these “failures” are more to do with parents’ re-

consulting behaviour unaware of the duration of common RTI illness (30); the inclination of the clinician to prescribe an antibiotic in children because of diagnostic uncertainty coupled with concern that the disease might progress (31); that unnecessary antibiotic use in young children disturbs the fragile microbiome with subsequent increased susceptibility to infection (32); or that antibiotic-resistant infections could have an important role to play in leading to “response failures”.(33)

Recent prospective evidence in infants suggests that routinely used antibiotics may have more prolonged consequences for microbiota-driven resilience against RTIs than currently is thought, by depleting certain protective bacterial species in the respiratory microbiome.(32) Therefore antibiotics, in addition to other environmental drivers (e.g. crowding in day care settings, number of siblings), may affect resilience against RTIs over time.

As outlined in Chapter 2, the relationship between antibiotic exposure, resistance and outcomes is complex. This complexity depends on a number of factors such as the pattern of antibiotic use, the specific interaction between bacterium and drug, the potential for transmission, measuring resistance at different time points, and the stage the country is at in the evolution of resistance (see section 2.8.2).(34, 35) The available evidence of an association between antibiotic exposure and resistance in relation to respiratory bacteria in symptomatic children is limited. For example, if we consider the most common bacterial pathogen causing community-acquired LRTIs (36), *Streptococcus pneumoniae*, there is some evidence of an association between antibiotics and resistance between 0 and 12 months based on four retrospective studies examining resistant *Streptococcus pneumoniae* carriage in symptomatic children with acute RTI.(37-40) However, this association was less clear at time periods between these points.

Other evidence, based on findings from a nested study in adults with community-acquired lower RTIs receiving amoxicillin, showed that the potential for selection of resistant *Streptococcus pneumoniae*, and its persistence *in vivo* is likely to be modest and short-lived, and was no longer significant at days 28–35.(41) Taking another common respiratory bacterium in children,

Haemophilus influenzae, the risk of recovering a β lactamase encoding resistance element among nasopharyngeal *Haemophilus* species from that child's throat two weeks later doubled in a prospective study of 119 children (aged 6 months to 12 years) prescribed amoxicillin for either otitis media or a suspected respiratory infection.(42) Therefore, the effect of antibiotic resistance is likely to impact earlier in the recovery period e.g. within 14 days of initial antibiotic course as observed in Chapter 5 where children received mostly broad-spectrum penicillin for acute RTIs. However, the overall proportion of children with acute RTI whose re-attendance is explained by antibiotic-resistant bacterial infection is likely to be low (because most RTIs in this age group are viral). If we apply these findings to those from Chapter 4 where the association of resistant bacteria and response failure was examined, the impact of antibiotic resistance may have a greater contribution to clinical response failures in children than what was observed in adults from the GRACE (Genomics to combat Antimicrobial Resistance in Community-acquired LRTI in Europe (www.grace-lrti.org) study where bacterial resistance would only account for treatment failure in less than 2% of adult patients (within 30 days of their initial prescription).(43)

7.2.3 Parents' perceptions of antibiotic use and antibiotic resistance in the community

The initial two themes in Chapter 6 complement previous qualitative research with parents in primary care. (27, 44-49) Parents understandably worry about the possibility of serious illness when their young child is acutely unwell. There is also uncertainty and anxiety surrounding their decision to seek medical help. Parents will seek safety in the face of uncertainty, and they will take opportunities to receive timely treatment for symptoms to minimise the risk of infection-related complications that require hospital admission. The findings are consistent with other studies that show that parents seek information from a wide range of sources about RTIs in children, and are less confident about self-management strategies at home.(36, 50)

The findings in Chapter 6 confirmed that most parents entrust their clinician to decide when antibiotics are needed and placed value on the physical examination of the child, as observed in

previous studies.(36, 51-55) However, in this study there were some parents who expressed unease about blindly trusting the clinician to make this decision and wanted to be in a better position to discuss the appropriateness of antibiotics for their child with their GP. This finding has recently been echoed in a study in the UK.(49)

Parents' reticence towards antibiotics for their children centred around the potential of antibiotics to alter the child's gut flora, concerns about adverse effects associated with taking drugs (e.g. allergic reactions; side-effects in particular gastrointestinal upset), and concerns about antibiotics weakening the immune system, as observed in previous studies.(30, 54, 56) However in this study, there was also a clear group of parents that were unaware of any side-effects or risk associated with antibiotics or had few concerns about adverse effects, resonating with the findings of a recent study.(49)

Very few parents linked antibiotic resistance (or their interpretation thereof) as a potential harm of antibiotics. This is in contrast to other studies where parents' reluctance to use antibiotics clearly stemmed from their worries about the development of antibiotic resistance.(30, 53) However, the findings of those studies may have been influenced by inclusion of better educated participants, choice of different qualitative research methods e.g. computer-assisted telephone interview survey (30) or focus groups dominated by a "self-proclaimed expert" that stifled other participants' views.(53)

The findings in Chapter 6 showed that most parents were aware of the term "antibiotic resistance". Yet, they acknowledged a lack of depth in their understanding of the concept of antibiotic resistance in keeping with a recent UK study.(49) This would also explain why their interpretations of the term "antibiotic resistance" were often at odds with scientific understanding (57). Most parents in this study, however, held similar beliefs to other parents from other studies that supported reducing antibiotic prescribing and that antibiotics should be reserved for infections they perceived to be severe or for troublesome symptoms such as earache.(53, 58)

The majority of parents did not link their individual or families' consumption of antibiotics to the development of antibiotic resistance in the community, reaffirming findings from previous studies. (59, 60) Parents did not consider their families at risk of antibiotic resistance because that they considered themselves "low-users" of antibiotics reiterating findings from a recent study in the USA where parents were not worried about resistance because their children took antibiotics "maybe twice a year".(54) They primarily personalised the risk of antibiotic resistance to the individual, and reflected little on the extent to which antibiotic resistance is a community problem where resistant bacteria are spread and transmitted in communal areas such as nurseries.

Some parents were happy to relax stringent hygiene measures for their child in the belief that exposure to organisms would boost their child's immunity and reduce the chances of antibiotic resistance. These parents also perceived that using household antibacterial cleaning products promotes antibiotic resistance. This may tie in with evolving evidence that certain household antibacterial soaps could be an emerging risk factor for antibiotic resistance in the community.(61-63) Yet, this may be misconstrued as being in direct conflict with current public health messages promoting the importance of hand hygiene.(64).

The findings of this study were consistent with other studies where parents suggested that limiting antibiotic use in (other) patients, and completing antibiotic courses was important to stem the tide of antibiotic resistance.(59, 60) Others felt that antibiotic resistance was "much bigger" for an individual to tackle echoing previous studies.(59, 60) However, parents did not propose to reduce their own families' antibiotic use.

None of the parents interviewed had seen examples of a current public antibiotic awareness campaign (Antibiotic Guardian) launched in November 2014 and widely disseminated through various channels in primary and secondary care within the NHS, public health, professional organizations, social media and traditional media press releases.(65, 66) This would be consistent with a process evaluation of the UK-wide Antibiotic Guardian campaign where only a third of those who signed up to the online pledge were members of the public.(65)

Parents were prepared to use fewer antibiotics for their children having read through the Antibiotic Guardian leaflet. Some parents did not welcome the negative advertising associated with promoting the gravity of antibiotic resistance which can both help and hinder mass communication.(67) Rather parents wanted better public campaign strategies on antibiotic resistance using a universal message that has a personal message for them and their families that fits into their daily lives. This has been shown to influence direct personal engagement when implementing health-based behaviour change in other public health interventions e.g. hand hygiene at home.(68, 69) Parents wanted clinicians in the community to have better diagnostic tests at hand, more transparent exchange of information about whether antibiotics were needed, and information about alternative non-antibiotic treatment strategies as highlighted in other studies.(51, 52, 70-72)

7.3 Implications of findings for clinical practice

This thesis demonstrates that most parents, as a subset of the general population, are aware of the term “antibiotic resistance” and mostly recognise its importance: treatment failure, severe infection, hospitalisation and death (Chapter 6). However, because our scientific understanding about community factors that contribute to antibiotic resistance is unclear, limited and at times confusing, it is no wonder parents wrestle with the correct scientific understanding of antibiotic resistance and what it means for them. Clinicians too, grapple between the decisions to prescribe (thereby lowering an individual patient coming to harm) versus not prescribing (lowering community risk) and perceive that their prescribing decisions have little clinical impact in the community.(73, 74) This thesis, however, presents novel evidence that the decision to prescribe an antibiotic (or not) for common infections in the community has implications for individual patients (Chapter 4). Clinicians therefore need to inform patients that unnecessary antibiotics are harmful, even for common infections.

Firstly, the findings in Chapter 5 challenge the perception that every day antibiotic prescribing decisions for young children do not have unintended or adverse consequences. GPs need to be

cautious and take into account previous antibiotic exposure when considering prescribing an antibiotic for acute RTI in childhood. For example, a parent's claim that "antibiotic X always works for my child"(75), now needs to be balanced with the likelihood that preschool children who have received two or more antibiotic courses for acute RTIs within the previous year are less likely to respond to an antibiotic the next time they have an acute RTI. Therefore, incorporating these findings into clinical practice guidelines and decision-support systems in primary care will give GPs and parents better evidence to support a non-antibiotic strategy.(76, 77) Examples of candidate decision-support systems include the RCGP's TARGET Antibiotics Toolkit and AccuRx.(77, 78) Indirectly, this can help curb expectations for antibiotics (79), and facilitate shared-decision making during consultations.(80)

Secondly, the findings in Chapter 4 demonstrate that antibiotic resistance significantly impacts on patients' illness burden in the community and that every day antibiotic prescribing decisions for common infections are important. Bearing in mind that antibiotics are the greatest driver for developing an antibiotic-resistant infection, these findings support the need to better identify patients who might benefit from antibiotic treatment. This means rapid diagnostics for antibiotic resistance and other prognostic tools to reduce clinical uncertainty need to be promoted and evaluated in community settings to better identify patients who might need antibiotics, and to avoid or reduce the risk of antibiotic response failures. Early evidence suggests that rapid diagnostics used in community settings can guide antibiotic prescribing for community-acquired pneumonia (81), and trials are underway for UTIs.(82, 83) Similarly, prognostic tools to reduce clinical uncertainty like *STARWAVE* and acute cough in children (26), can give clinicians better insight which children are more likely to require hospital admission for acute RTIs and indirectly, could be used to reduce antibiotic prescriptions in primary care for children at very low risk. Yet, GPs prescribing fewer antibiotics also need to be able to demonstrate that they are contributing to the goal of reducing antibiotic resistance with clear health benefits for their patients. This would require longer-term trials to demonstrate that using fewer antibiotics in children is beneficial.

Thirdly, for clinicians, relating the estimates in Chapter 4 to relative risk, clinical response failure is almost three times more likely in patients with antibiotic-resistant *E. coli* UTIs and around two times more likely in patients with antibiotic-resistant *S. pneumoniae* CAP and AOM than in patients whose infections are antibiotic-sensitive based on the odds ratio (OR) estimate and median clinical response failure rate (*E. coli* UTI: relative risk 2·96, OR 4·19, median failure rate 13% [range 9% to 32%](84-91); *S. pneumoniae* CAP: relative risk 1·97, OR 2·15, median failure rate of 8% [4-50%](92-96); and *S. pneumoniae* AOM: relative risk 2·18, OR 2·51, median failure rate of 10% [4-16%]).(96-100) Expressing such consequences in a manner that is more meaningful is supported by a recent report from the Academy of Medical Sciences report (Enhancing the use of scientific evidence to judge the potential benefits and harms of medicine).(101, 102) This is important especially where decisions about whether to start antibiotics may not be clear cut and will help health care professionals explain the potential implications of unnecessary antibiotic use and antibiotic-resistant infections.

Finally, to facilitate better informed decision-making about the implications of unnecessary antibiotic use and antibiotic resistance, the decision to prescribe antibiotics should be a shared decision between clinician and parent/carer.(80, 103) However, making a shared decision about the risk/benefit of antibiotics and the consequences of antibiotic-resistant infections should be based on tangible outcomes that patients and primary care clinicians can grasp and relate to. An example of such an outcome (Chapter 5) that is likely more meaningful to parents is that higher levels of antibiotic exposure in preschool children with acute RTIs is associated with an increased likelihood of subsequent RTIs not responding to antibiotic treatment. This means that GPs may need to spend more time listening and addressing the worries of parents, explaining antibiotic resistance and the consequences of unnecessary antibiotic use, to reduce antibiotic prescribing without reducing patient satisfaction.(104)

7.4 Implications of findings for policy

Health policy related to appropriate antibiotic prescribing and antibiotic resistance should refocus its agenda by showing that antibiotic resistance has an adverse impact on patients' recovery from common infections in the community (Chapter 4). Antibiotic resistance is a community problem that can potentially affect everybody living in the community. Community antibiotic resistance surveillance systems are one example of giving clinicians some guidance in terms of antibiotic strategy to improve the appropriateness of prescribing.(105) However, quality indicators that focus on the diagnostic process are also needed for common infections, similar to those successfully employed in chronic diseases like diabetes and cardiovascular diseases, to improve the appropriateness of antibiotic prescribing and complement current financial incentives in primary care to reduce overall antibiotic prescribing.(106) This will likely include better diagnostic information and unbiased denominators taking into account changes in diagnostic methods and disease classification and confounding by indication. However, diagnostic indicators should focus more on acute RTIs, which is the most frequent type of infection in primary care and where the majority of unnecessary antibiotic prescribing occurs. This is highlighted by a recent systematic review where the majority of identified quality indicators focused on the choice of antibiotic (72%) rather than the diagnostic process leading to a diagnosis (6%) and the decision to prescribe an antibiotic (22%).(107)

As outlined in Chapter 2, public health messages around antibiotic stewardship (including the use of digital technology and social media) have not had the desired effect in the community suggesting that we need to rethink our current strategy. In the first instance, educational materials and antibiotic awareness campaigns need to be tailored to reach their intended audiences. This means antibiotic awareness messages aimed at parents need to fit into their busy lives in a format that they will engage with, by displaying information quickly, clearly and reliably. Novel ways of intervention are needed to help improve public engagement with advice on using self-care strategies and disseminating a universal message about the implications of unnecessary antibiotic use. One example, aimed at parents of preschool children, might be the development of a series of

evidence-based infographics around antibiotics and the implications of unnecessary antibiotic use, displayed on everyday household consumer goods (e.g. nappies) or antibiotic packets. Evidence-based infographics have already been employed to support healthcare professionals to promote physical activity behaviour change (108), and more recently targeting pregnant women.(109) One advantage of using this visual approach would be that the same message can be tailored to different geographic regions, languages and societies, or for those parts of the world where antibiotics can be obtained without prescription. Chapter 6 reiterates that simple, clear and unambiguous terminology such as “superbugs” or “drug-resistant infections” are needed for antibiotic awareness campaigns to encourage parent engagement with health messages.(57) This needs to be coupled with a message that demonstrates a clear consequence of antibiotic resistance that has personal relevance for parents and their families.

Lastly, policy makers should also carefully consider the introduction of concurrent national public health campaigns that can be construed to be conflicting e.g. sepsis campaigns advocating early detection and antibiotic administration versus antibiotic awareness campaigns encouraging self-care and promoting the use of fewer antibiotics. Likewise, there should also be an awareness that hospital-derived antibiotic stewardship measures e.g. hand hygiene and infection control, might compete with parents’ mistaken beliefs of being less “hygienic” to promote a young child’s developing microbiome; or conversely, their beliefs that the use of anti-bacterial cleaning agents at home will reduce the risk of antibiotic resistance.

7.5 Implications of findings for future research

The most effective and acceptable interventions to reduce inappropriate antibiotic prescribing target parents and clinicians during consultations, using a shared-decision approach and are grounded in behaviour change theory.(103) This thesis clearly quantifies for parents the risks versus benefits of using antibiotics for acute RTIs which are mostly self-limiting (Chapter 5) and may help parents better understand the reasons for avoiding antibiotics in these situations. These findings now need to be incorporated and tested in a larger programme of research by: (a)

developing a novel public health (or general practice-based) complex intervention to promote more appropriate patient behaviour in relation to antibiotic use; (b) assessing the effectiveness of this intervention using a cluster randomised controlled trial; (c) evaluating the implementation of the intervention using mixed methods; and (d) evaluating the cost-effectiveness of the intervention. Examples include evaluating a decision support system $\pm$ microbial point-of-care testing in general practice, or an online app-based service for automatically diagnosing UTIs and antibiotic prescribing in the community.

Yet, given the paucity of studies for some infections in Chapter 4, further evidence is needed to determine the clinical relevance of antibiotic resistance for skin and other common infections in the community. Importantly, these need to relate to patient outcomes, and not simply the association between antibiotic use and microbiological outcome. In addition, more research is needed in relation to direct health care resource utilisation and socioeconomic burden (e.g. days off work) associated with antibiotic-resistant infections in the community.⁽¹¹⁰⁾ This will mean looking more broadly at the impact of unnecessary antibiotic use on families and the wider community. One example might be to further explore the relevance of antibiotic “response failure” in household members using a similar database like in Chapter 5. Although there are inherent limitations with routinely collected data (e.g. in terms of defining and interpreting response failure events), this example would associate one’s personal antibiotic consumption with potential household and social benefit. This would reinforce that bacteria are spread from person to person in the community and bring home the impact of unnecessary antibiotic use and antibiotic resistance to households in the community.

Thirdly, health slogans to complete the antibiotic course and its potential impact on resistance need further scrutiny.^(111, 112) Although there is early evidence to (re)evaluate the optimal length of antibiotic courses for common infections ⁽¹¹³⁾, we need to correlate this to specific bacteria, and the effect of not completing a full course of antibiotics on resistance and clinical outcome.

Fourthly, as outlined in Chapter 5, routinely collected primary care data in its current format is unable to tease out the intricacies of everyday prescribing decisions. Large-scale observational studies in primary care settings are therefore needed to determine the proportion of clinical response failures for common infections that are indeed attributable to antibiotic resistance. Future work also needs to develop a better understanding of the relationship between antibiotic prescribing levels and development of clinically significant antibiotic resistance in the community.

Future initiatives should incorporate the unintended consequences (harms) of antibiotics and antibiotic resistance into parents' decision-making process to use antibiotics for their child. This can be achieved through discrete choice experiments, for example, by further exploring how parents trade-off on factors influencing antibiotic use for their child.(114)

Lastly, community interventions need to explore the influence of culture and context on antibiotic use. Such factors may be a barrier in transferring effective interventions from one context or country to another, especially in low and middle-income countries.

7.6 Final reflections of thesis

While the findings from this thesis provide an important and original contribution to research about the impact of antibiotic resistance and antibiotic stewardship as it relates to primary care, it poses many more questions and avenues for further research, as outlined above.

Through this program of research, I have had the opportunity to learn and utilise new research methods e.g. multivariable logistic regression using a three-level mixed effects model (Chapter 5), and also to refine and improve my systematic review (Chapter 4) and qualitative research skills (Chapter 6). These skills are essential for a mixed-methods researcher.

In each of three studies, I have been aware of the strengths and limitations and cautious about over-interpreting findings (see discussions in the individual chapters). Likewise, there are some areas, with the benefit of hindsight, where I would have planned things differently. One example

from the database study in Chapter 5 would have been to include all oral antibiotic prescriptions in preschool children as antibiotic exposure (and not simply those associated with an RTI diagnostic code). During the course of data management, it became evident that a substantial proportion of children (62%; 31,027/49,973) had received antibiotic prescriptions in the 12 months prior to the index date for indications not captured under my extensive list of RTI codes. This was quite unexpected. We had anticipated that an acute RTI would by far be the most common reason for which an antibiotic is prescribed in young children. This affected our original sample size calculation and highlighted the limitations of routinely collected data. Closer inspection showed that these antibiotics were prescribed for other respiratory conditions e.g. childhood wheeze, where current NICE guidelines advise a non-antibiotic strategy and other non-RTI infections e.g. urinary tract infection where an antibiotic is entirely appropriate. However, from a clinical point of view, all antibiotics have the potential to disrupt the human microbiome regardless of indication or whether the antibiotic was appropriately prescribed or not. Therefore, analysing the potential effect of all antibiotic exposure in childhood regardless of indication is an important public health question that a similar dataset could answer. Another example, from Chapter 6, was that the most effective recruitment method was through local baby/toddler groups in the community and not as anticipated through GP practices. For future similar studies, it might be worth focussing on these community networks of baby/toddler groups because GP practice recruitment was time-consuming, and proved to be much less effective. Finally, there are two outstanding publications from this thesis and Chapters 5 and 6 will form the backbone of these publications within the near future.

7.7 Conclusions

The key implications of this thesis for clinical practice are that previous antibiotic exposure in preschool children needs to be incorporated into clinical practice guidelines and decision-support systems to help clinicians and parents consider a non-antibiotic strategy for acute RTIs. We also need to better identify patients who might need an antibiotic by promoting and evaluating rapid

diagnostic tests or further prognostic tools in the community to avoid or reduce the risk of antibiotic response failures.

For policy, we need to concentrate efforts in primary care by emphasising that antibiotic resistance is a community problem. This means creating tailored educational materials and antibiotic awareness campaigns aiming to optimise antibiotic use on outcomes that people can relate to and ensure they reach their intended audience. These messages need to be universal and convenient, summarising information quickly, clearly and reliably. In addition, community antibiotic resistance surveillance systems and quality indicators that focus on the diagnostic process for common infections are needed to improve the appropriateness of antibiotic prescribing.

Future initiatives should include a novel public health (or general practice-based) complex intervention to evaluate this thesis' findings, assess the clinical relevance of antibiotic resistance for other common infections in primary care, and determine the relative contribution of antibiotic resistance to clinically-defined response failures for common infections.

7.8 References

1. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC infectious diseases*. 2014;14:13.
2. Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2016;352:i939.
3. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2010;340:c2096.
4. Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. *Scandinavian journal of primary health care*. 2007;25(1):49-57.
5. Gagyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. *BMJ (Clinical research ed)*. 2015;351:h6544.
6. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients. *The Cochrane database of systematic reviews*. 2014;10:Cd002109.

7. Tahtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *The New England journal of medicine*. 2011;364(2):116-26.
8. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews*. 2015(6).
9. Fahey T, Webb E, Montgomery AA, Heyderman RS. Clinical management of urinary tract infection in women: a prospective cohort study. *Family practice*. 2003;20(1):1-6.
10. Little P, Turner S, Rumsby K, Warner G, Moore M. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort, and qualitative study. *Health Technology Assessment*. 2009;13(19):96.
11. Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2015;65(639):e702-7.
12. Hooton TM, Scholes D, Hughes JP, Winter C, Roberts PL, Stapleton AE, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. *The New England journal of medicine*. 1996;335(7):468-74.
13. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2015.
14. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax*. 2012;67(1):71-9.
15. Bean DC, Krahe D, Wareham DW. Antimicrobial resistance in community and nosocomial *Escherichia coli* urinary tract isolates, London 2005-2006. *Annals of clinical microbiology and antimicrobials*. 2008;7:13.
16. Farrell DJ, Morrissey I, De Rubeis D, Robbins M, Felmingham D. A UK multicentre study of the antimicrobial susceptibility of bacterial pathogens causing urinary tract infection. *The Journal of infection*. 2003;46(2):94-100.
17. Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, Sahm DF. Trends in antimicrobial resistance among urinary tract infection isolates of *Escherichia coli* from female outpatients in the United States. *Antimicrobial agents and chemotherapy*. 2002;46(8):2540-5.
18. Kronenberg A, Koenig S, Droz S, Muhlemann K. Active surveillance of antibiotic resistance prevalence in urinary tract and skin infections in the outpatient setting. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2011;17(12):1845-51.
19. Gotfried MH. Epidemiology of clinically diagnosed community-acquired pneumonia in the primary care setting: results from the 1999-2000 respiratory surveillance program. *The American journal of medicine*. 2001;111 Suppl 9A:25S-9S; discussion 36S-8S.
20. Morrissey I, Robbins M, Viljoen L, Brown DF. Antimicrobial susceptibility of community-acquired respiratory tract pathogens in the UK during 2002/3 determined locally and centrally by BSAC methods. *The Journal of antimicrobial chemotherapy*. 2005;55(2):200-8.
21. Angoulvant F, Cohen R, Doit C, Elbez A, Werner A, Bechet S, et al. Trends in antibiotic resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* isolated from nasopharyngeal flora in children with acute otitis media in France before and after 13 valent pneumococcal conjugate vaccine introduction. *BMC infectious diseases*. 2015;15:236.
22. Farrell DJ, Klugman KP, Pichichero M. Increased antimicrobial resistance among nonvaccine serotypes of *Streptococcus pneumoniae* in the pediatric population after the introduction of 7-valent pneumococcal vaccine in the United States. *The Pediatric infectious disease journal*. 2007;26(2):123-8.
23. Berni E, Scott LA, Jenkins-Jones S, De Voogd H, Rocha MS, Butler CC, et al. Non-Response to Antibiotic Treatment in Adolescents for Four Common Infections in UK Primary Care 1991-2012: A Retrospective, Longitudinal Study. *Antibiotics (Basel, Switzerland)*. 2016;5(3).

24. Currie CJ, Berni E, Jenkins-Jones S, Poole CD, Ouwens M, Driessen S, et al. Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. *BMJ (Clinical research ed)*. 2014;349:g5493.
25. McGrath LJ, Becker-Dreps S, Pate V, Brookhart MA. Trends in antibiotic treatment of acute otitis media and treatment failure in children, 2000-2011. *PloS one*. 2013;8(12):e81210.
26. Hay AD, Redmond NM, Turnbull S, Christensen H, Thornton H, Little P, et al. Development and internal validation of a clinical rule to improve antibiotic use in children presenting to primary care with acute respiratory tract infection and cough: a prognostic cohort study. *The Lancet Respiratory medicine*. 2016;4(11):902-10.
27. Cabral C, Lucas PJ, Ingram J, Hay AD, Horwood J. "It's safer to ..." parent consulting and clinician antibiotic prescribing decisions for children with respiratory tract infections: An analysis across four qualitative studies. *Soc Sci Med*. 2015;136-137:156-64.
28. Falagas ME, Mourtzoukou EG, Vardakas KZ. Sex differences in the incidence and severity of respiratory tract infections. *Respiratory Medicine*. 2007;101(9):1845-63.
29. Muenchhoff M, Goulder PJ. Sex differences in pediatric infectious diseases. *The Journal of infectious diseases*. 2014;209 Suppl 3:S120-6.
30. Coxeter PD, Mar CD, Hoffmann TC. Parents' Expectations and Experiences of Antibiotics for Acute Respiratory Infections in Primary Care. *Annals of family medicine*. 2017;15(2):149-54.
31. Fletcher-Lartey S, Yee M, Gaarslev C, Khan R. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. *BMJ open*. 2016;6(10):e012244.
32. Bosch AA, de Steenhuijsen Pijters WA, van Houten MA, Chu M, Biesbroek G, Kool J, et al. Maturation of the Infant Respiratory Microbiota, Environmental Drivers and Health Consequences: A Prospective Cohort Study. *American journal of respiratory and critical care medicine*. 2017.
33. Van Hecke O, Wang K, Lee JJ, Roberts NW, Butler CC. The implications of antibiotic resistance for patients' recovery from common infections in the community: a systematic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2017.
34. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005;365(9459):579-87.
35. Turnidge J, Christiansen K. Antibiotic use and resistance--proving the obvious. *Lancet*. 2005;365(9459):548-9.
36. de Bont EG, Loonen N, Hendrix DA, Lepot JM, Dinant GJ, Cals JW. Childhood fever: a qualitative study on parents' expectations and experiences during general practice out-of-hours care consultations. *BMC family practice*. 2015;16:131.
37. Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ (Clinical research ed)*. 1996;313(7054):387-91.
38. Ghaffar F, Muniz LS, Katz K, Smith JL, Shouse T, Davis P, et al. Effects of large dosages of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of *Streptococcus pneumoniae*, *Haemophilus influenzae*, nonpneumococcal alpha-hemolytic streptococci, and *Staphylococcus aureus* in children with acute otitis media. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2002;34(10):1301-9.
39. Samore MH, Magill MK, Alder SC, Severina E, Morrison-De Boer L, Lyon JL, et al. High rates of multiple antibiotic resistance in *Streptococcus pneumoniae* from healthy children living in isolated rural communities: association with cephalosporin use and intrafamilial transmission. *Pediatrics*. 2001;108(4):856-65.
40. Schrag SJ, Pena C, Fernandez J, Sanchez J, Gomez V, Perez E, et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. *Jama*. 2001;286(1):49-56.
41. Malhotra-Kumar S, Van Heirstraeten L, Coenen S, Lammens C, Adriaenssens N, Kowalczyk A, et al. Impact of amoxicillin therapy on resistance selection in patients with

- community-acquired lower respiratory tract infections: a randomized, placebo-controlled study. *The Journal of antimicrobial chemotherapy*. 2016;71(11):3258-67.
42. Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R, et al. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ (Clinical research ed)*. 2007;335(7617):429.
 43. Coenen S, Goossens H. Antibiotic treatment failure in primary care. *BMJ (Clinical research ed)*. 2014;349:g5970.
 44. Francis NA, Crocker JC, Gamper A, Brookes-Howell L, Powell C, Butler CC. Missed opportunities for earlier treatment? A qualitative interview study with parents of children admitted to hospital with serious respiratory tract infections. *Archives of disease in childhood*. 2011;96(2):154-9.
 45. Hansen MP, Howlett J, Del Mar C, Hoffmann TC. Parents' beliefs and knowledge about the management of acute otitis media: a qualitative study. *BMC family practice*. 2015;16:82.
 46. Kai J. What worries parents when their preschool children are acutely ill, and why: a qualitative study. *BMJ (Clinical research ed)*. 1996;313(7063):983-6.
 47. Neill SJ, Jones CH, Lakhanpaul M, Roland DT, Thompson MJ. Parents' help-seeking behaviours during acute childhood illness at home: A contribution to explanatory theory. *Journal of child health care : for professionals working with children in the hospital and community*. 2016;20(1):77-86.
 48. Sharma M, Usherwood T. Up close - reasons why parents attend their general practitioner when their child is sick. *Australian family physician*. 2014;43(4):223-6.
 49. Halls A, van't Hoff C, Little P, Verheij T, Leydon GM. Qualitative interview study of parents' perspectives, concerns and experiences of the management of lower respiratory tract infections in children in primary care. *BMJ open*. 2017;7(9).
 50. Ingram J, Cabral C, Hay AD, Lucas PJ, Horwood J. Parents' information needs, self-efficacy and influences on consulting for childhood respiratory tract infections: a qualitative study. *BMC family practice*. 2013;14:106.
 51. Brookes-Howell L, Wood F, Verheij T, Prout H, Cooper L, Hood K, et al. Trust, openness and continuity of care influence acceptance of antibiotics for children with respiratory tract infections: a four country qualitative study. *Family practice*. 2014;31(1):102-10.
 52. Cabral C, Ingram J, Hay AD, Horwood J. "They just say everything's a virus" --parent's judgment of the credibility of clinician communication in primary care consultations for respiratory tract infections in children: a qualitative study. *Patient education and counseling*. 2014;95(2):248-53.
 53. Finkelstein JA, Dutta-Linn M, Meyer R, Goldman R. Childhood infections, antibiotics, and resistance: what are parents saying now? *Clinical pediatrics*. 2014;53(2):145-50.
 54. Szymczak JE, Klieger SB, Miller M, Fiks AG, Gerber JS. What Parents Think About the Risks and Benefits of Antibiotics for Their Child's Acute Respiratory Tract Infection. *Journal of the Pediatric Infectious Diseases Society*. 2017.
 55. Dekker ARJ, Verheij TJM, van der Velden AW. Antibiotic management of children with infectious diseases in Dutch Primary Care. *Family practice*. 2017;34(2):169-74.
 56. Jonsson H, Haraldsson RH. Parents' perspectives on otitis media and antibiotics. A qualitative study. *Scandinavian journal of primary health care*. 2002;20(1):35-9.
 57. Mendelson M, Balasegaram M, Jinks T, Pulcini C, Sharland M. Antibiotic resistance has a language problem. *Nature*. 2017;545(7652):23-5.
 58. Cabral C, Ingram J, Lucas PJ, Redmond NM, Kai J, Hay AD, et al. Influence of Clinical Communication on Parents' Antibiotic Expectations for Children With Respiratory Tract Infections. *Annals of family medicine*. 2016;14(2):141-7.
 59. Brooks L, Shaw A, Sharp D, Hay AD. Towards a better understanding of patients' perspectives of antibiotic resistance and MRSA: a qualitative study. *Family practice*. 2008;25(5):341-8.
 60. McCullough AR, Parekh S, Rathbone J, Del Mar CB, Hoffmann TC. A systematic review of the public's knowledge and beliefs about antibiotic resistance. *The Journal of antimicrobial chemotherapy*. 2016;71(1):27-33.

61. Aiello AE, Larson E. Antibacterial cleaning and hygiene products as an emerging risk factor for antibiotic resistance in the community. *The Lancet Infectious diseases*. 2003;3(8):501-6.
62. Aiello AE, Larson EL, Levy SB. Consumer antibacterial soaps: effective or just risky? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2007;45 Suppl 2:S137-47.
63. Giuliano CA, Rybak MJ. Efficacy of triclosan as an antimicrobial hand soap and its potential impact on antimicrobial resistance: a focused review. *Pharmacotherapy*. 2015;35(3):328-36.
64. National Institute for Health and Care Excellence. Antimicrobial stewardship: changing risk-related behaviours in the general population. NICE; 2017.
65. Bhattacharya A, Hopkins S, Sallis A, Budd EL, Ashiru-Oredope D. A process evaluation of the UK-wide Antibiotic Guardian campaign: developing engagement on antimicrobial resistance. *Journal of Public Health*. 2017;39(2):e40-e7.
66. Department of Health. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. London; 2013.
67. Apollonio DE, Malone RE. Turning negative into positive: public health mass media campaigns and negative advertising. *Health Education Research*. 2009;24(3):483-95.
68. Little P, Stuart B, Hobbs FD, Moore M, Barnett J, Popoola D, et al. An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial. *Lancet*. 2015;386(10004):1631-9.
69. Yardley L, Miller S, Schlotz W, Little P. Evaluation of a Web-based intervention to promote hand hygiene: exploratory randomized controlled trial. *Journal of medical Internet research*. 2011;13(4):e107.
70. Mangione-Smith R, Zhou C, Robinson JD, Taylor JA, Elliott MN, Heritage J. Communication practices and antibiotic use for acute respiratory tract infections in children. *Annals of family medicine*. 2015;13(3):221-7.
71. Van den Bruel A, Jones C, Thompson M, Mant D. C-reactive protein point-of-care testing in acutely ill children: a mixed methods study in primary care. *Archives of disease in childhood*. 2016;101(4):382-6.
72. Wood F, Brookes-Howell L, Hood K, Cooper L, Verheij T, Goossens H, et al. A multi-country qualitative study of clinicians' and patients' views on point of care tests for lower respiratory tract infection. *Family practice*. 2011;28(6):661-9.
73. McCullough AR, Rathbone J, Parekh S, Hoffmann TC, Del Mar CB. Not in my backyard: a systematic review of clinicians' knowledge and beliefs about antibiotic resistance. *The Journal of antimicrobial chemotherapy*. 2015;70(9):2465-73.
74. Wood F, Phillips C, Brookes-Howell L, Hood K, Verheij T, Coenen S, et al. Primary care clinicians' perceptions of antibiotic resistance: a multi-country qualitative interview study. *The Journal of antimicrobial chemotherapy*. 2013;68(1):237-43.
75. Russell G. Antibiotic resistance in children with E coli urinary tract infection. *BMJ (Clinical research ed)*. 2016;352:i1399.
76. Tonkin-Crine S, Yardley L, Little P. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. *The Journal of antimicrobial chemotherapy*. 2011;66(10):2215-23.
77. AccuRx. Eliminate inappropriate antibiotic use 2017 [Available from: <http://www.accurx.com/>].
78. Antimicrobial Stewardship in Primary Care (ASPIC). TARGET Antibiotics Toolkit 2017 [Available from: <http://www.rcgp.org.uk/TARGETantibiotics>].
79. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implementation science : IS*. 2012;7:37.
80. Coxeter P, Del Mar CB, McGregor L, Beller EM, Hoffmann TC. Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. *The Cochrane database of systematic reviews*. 2015;11:Cd010907.

81. Minnaard MC, van de Pol AC, Hopstaken RM, van Delft S, Broekhuizen BD, Verheij TJ, et al. C-reactive protein point-of-care testing and associated antibiotic prescribing. *Family practice*. 2016.
82. Bates J, Thomas-Jones E, Pickles T, Kirby N, Gal M, Bongard E, et al. Point of care testing for urinary tract infection in primary care (POETIC): protocol for a randomised controlled trial of the clinical and cost effectiveness of FLEXICULT informed management of uncomplicated UTI in primary care. *BMC family practice*. 2014;15:187.
83. Holm A, Cordoba G, Sorensen TM, Jessen LR, Siersma V, Bjerrum L. Point of care susceptibility testing in primary care - does it lead to a more appropriate prescription of antibiotics in patients with uncomplicated urinary tract infections? Protocol for a randomized controlled trial. *BMC family practice*. 2015;16:106.
84. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with *E. coli* UTIs. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2006;56(530):686-92.
85. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Archives of internal medicine*. 2007;167(20):2207-12.
86. McNulty CA, Richards J, Livermore DM, Little P, Charlett A, Freeman E, et al. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *The Journal of antimicrobial chemotherapy*. 2006;58(5):1000-8.
87. Noskin GA, Zembower T, Chmielewski J, Tang P, La Rosa M, Peterson LR. Disappearance of the 'uncomplicated' urinary tract infection - The impact of emerging resistance. *Clinical Drug Investigation*. 2001;21:13-20.
88. Raz R, Chazan B, Kennes Y, Colodner R, Rottensterich E, Dan M, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2002;34(9):1165-9.
89. Soraas A, Sundsfjord A, Jorgensen SB, Liestol K, Jenum PA. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing *Escherichia coli*. *PloS one*. 2014;9(1):e85889.
90. Vallano A, Rodriguez D, Barcelo ME, Lopez A, Cano A, Vinado B, et al. [Antimicrobial susceptibility of uropathogens and outcome following antibiotic treatment for urinary tract infections in primary health care]. *Enfermedades infecciosas y microbiologia clinica*. 2006;24(7):418-25.
91. van Merode T, Nys S, Raets I, Stobberingh E. Acute uncomplicated lower urinary tract infections in general practice: clinical and microbiological cure rates after three- versus five-day treatment with trimethoprim. *The European journal of general practice*. 2005;11(2):55-8.
92. Hagberg L, Carbon C, van Rensburg DJ, Fogarty C, Dunbar L, Pullman J. Telithromycin in the treatment of community-acquired pneumonia: a pooled analysis. *Respir Med*. 2003;97(6):625-33.
93. O'Doherty B, Dutchman DA, Pettit R, Maroli A. Randomized, double-blind, comparative study of grepafloxacin and amoxycillin in the treatment of patients with community-acquired pneumonia. *The Journal of antimicrobial chemotherapy*. 1997;40 Suppl A:73-81.
94. van Rensburg DJ, Fogarty C, Kohno S, Dunbar L, Rangaraju M, Nusrat R. Efficacy of telithromycin in community-acquired pneumonia caused by pneumococci with reduced susceptibility to penicillin and/or erythromycin. *Chemotherapy*. 2005;51(4):186-92.
95. Yanagihara K, Otsu Y, Ohno H, Higashiyama Y, Miyazaki Y, Hirakata Y, et al. Clinical characteristics of pneumonia caused by penicillin resistant and sensitive *Streptococcus pneumoniae* in Japan. *Internal medicine (Tokyo, Japan)*. 2004;43(11):1029-33.
96. Zhanel GG, Wolter KD, Calciu C, Hogan P, Low DE, Weiss K, et al. Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant *Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data. *The Journal of antimicrobial chemotherapy*. 2014;69(10):2835-40.

97. Barry B, Gehanno P, Blumen M, Boucot I. Clinical outcome of acute otitis media caused by pneumococci with decreased susceptibility to penicillin. *Scandinavian journal of infectious diseases*. 1994;26(4):446-52.
98. Dagan R, Abramson O, Leibovitz E, Lang R, Goshen S, Greenberg D, et al. Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin. *The Pediatric infectious disease journal*. 1996;15(11):980-5.
99. Hoberman A, Dagan R, Leibovitz E, Rosenblut A, Johnson CE, Huff A, et al. Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. *The Pediatric infectious disease journal*. 2005;24(6):525-32.
100. Hoberman A, Paradise JL, Block S, Burch DJ, Jacobs MR, Balanescu MI. Efficacy of amoxicillin/clavulanate for acute otitis media: relation to *Streptococcus pneumoniae* susceptibility. *The Pediatric infectious disease journal*. 1996;15(10):955-62.
101. Freeman A, Marshall M, Treadwell J, Spiegelhalter D, Rafi I. Communicating risk in primary care: what the Academy of Medical Sciences' report means in practice. *British Journal of General Practice*. 2017;67(661):346-7.
102. Academy of Medical Sciences. Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines (AMS). 2017.
103. Tonkin-Crine SK, Tan PS, van Hecke O, Wang K, Roberts NW, McCullough A, et al. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. *The Cochrane database of systematic reviews*. 2017;9:Cd012252.
104. Lundkvist J, Akerlind I, Borgquist L, Molstad S. The more time spent on listening, the less time spent on prescribing antibiotics in general practice. *Family practice*. 2002;19(6):638-40.
105. Chin TL, McNulty C, Beck C, MacGowan A. Antimicrobial resistance surveillance in urinary tract infections in primary care. *The Journal of antimicrobial chemotherapy*. 2016;71(10):2723-8.
106. NHS England. Quality Premium guidance 2017-19 2017 [updated 11/08/2017. Available from: <https://www.england.nhs.uk/resources/resources-for-ccgs/ccg-out-tool/ccg-ois/qual-prem/>.
107. Saust LT, Monrad RN, Hansen MP, Arpi M, Bjerrum L. Quality assessment of diagnosis and antibiotic treatment of infectious diseases in primary care: a systematic review of quality indicators. *Scandinavian journal of primary health care*. 2016;34(3):258-66.
108. Department of Health. Start active, stay active: infographics on physical activity 2016 [Available from: <https://www.gov.uk/government/publications/start-active-stay-active-infographics-on-physical-activity>.
109. Smith R, Shakespeare J, Williams Z, Knight M, Foster C. Physical activity for pregnant women: an infographic for healthcare professionals. *British Journal of General Practice*. 2017;67(663):460-.
110. O'Neill J. Tackling Drug-Resistant Infections Globally: final report and recommendations. 2016 19 May 2016.
111. Gilbert GL. Knowing when to stop antibiotic therapy. *The Medical journal of Australia*. 2015;202(3):121-2.
112. Llewelyn MJ, Fitzpatrick JM, Darwin E, Sarah Tonkin C, Gorton C, Paul J, et al. The antibiotic course has had its day. *BMJ (Clinical research ed)*. 2017;358:j3418.
113. Moore M, Stuart B, Hobbs FR, Butler CC, Hay AD, Campbell J, et al. Influence of the duration of penicillin prescriptions on outcomes for acute sore throat in adults: the DESCARTE prospective cohort study in UK general practice. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2017;67(662):e623-e33.
114. Lum EP. Making decisions about antibiotic use in the Australian primary healthcare sector. Brisbane: Queensland University of Technology; 2017.

Page left intentionally blank

APPENDIX 1 – Search strategy of electronic databases for background literature review

A. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R): 1946- 7 November 2016

1	exp Drug Resistance, Bacterial/
2	((microbial* or bacterial*) adj3 resist*).ti,ab.
3	microb* or antibact* or anti-biotic* or anti-microb* or anti-bact*) adj3
4	1 or 2 or 3
5	(clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office).ti,ab.
6	4 and 5
7	exp animals/ not humans.sh.
8	6 not 7
9	limit 8 to "reviews (maximizes specificity)"
10	limit 8 to (comment or editorial or government publications or guideline or letter or news)

B. Embase: 1974 to 7 November 2016

1	antibiotic resistance/
2	drug resistance/ and exp antibiotic agent/
3	((microbial* or bacterial*) adj3 resist*).ti,ab.
4	((antibiotic* or antimicrob* or antibact* or anti-biotic* or anti-microb* or anti-bact*) adj3 resist*).ti,ab.
5	1 or 2 or 3 or 4
6	(clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office).ti,ab.
7	5 and 6
8	(exp animals/ or nonhuman/) not human/
9	7 not 8
10	limit 9 to "reviews (maximizes specificity)"
11	limit 7 to (editorial or letter or note or report)

C. Cochrane Central Register of Controlled Trials: Issue 11 of 12, November 2016

1	MeSH descriptor: [Drug Resistance, Bacterial] explode all trees
2	((antibiotic* or antimicrob* or antibact* or anti-biotic* or anti-microb* or anti-bact*) near resist*).ti,ab,kw (Word variations have been searched)
3	((microbial* or bacterial*) near resist*).ti,ab,kw
4	#1 or #2 or #3
5	clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office:ti,ab,kw (Word variations have been searched)

6	#4 and #5
---	-----------

D. Science Citation Index & Conference Proceedings Citation Index (Web of Science): 1945-7 November 2016

1	TOPIC: (((microbial* or bacterial*) NEAR/3 resistan*)) OR TOPIC: (((antibiotic* or antimicrob* or antibact* or anti-biotic* or anti-microb* or anti-bact*) NEAR/3 resistan*))
2	TS=((clinic OR clinics OR practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre OR centres or center or centers or office))
3	#2 AND #1
4	TI=("systematic review" OR meta-analys* OR metaanalys* OR "meta analys*")
5	#4 AND #3
6	#2 AND #1 Refined by: DOCUMENT TYPES: (NEWS ITEM OR LETTER OR EDITORIAL MATERIAL)

Total yield: 2,857 articles (Medline – 1,057; Embase CINAHL – 1,193; Cochrane Database of Systematic Reviews – 135; Web of Science Core Collection,– 472)

Total after duplicates removed: 1,741 articles

After screening of titles/abstracts: 156 articles

APPENDIX 2 – Search strategy of electronic databases for systematic review and meta-analysis

A. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R): 1946-16 April 2016

1	exp Drug Resistance, Bacterial/
2	((antibiotic or antimicrob* or anti-biot* or bact*) adj3 resistance).ti,ab.
3	1 or 2
4	(clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office).ab,ti.
5	Emergency service*.ab,ti.
6	(emergenc* adj3 (hospital* or department* or dept* or unit*1 or ward*1)).ab,ti.
7	("accident and emergency" or "accident & emergency" or a&e).ab,ti.
8	4 or 5 or 6 or 7
9	cellulitis/ or exp skin diseases, bacterial/ or soft tissue infections/
10	exp Respiratory Tract Infections/ or exp Otitis Media/
11	exp Urinary Tract Infections/
12	9 or 10 or 11
13	3 and 8 and 12
14	exp animals/ not humans/
15	13 not 14

B. Embase: 1974 to 15 April 2016

1	antibiotic resistance/
2	drug resistance/ and exp antibiotic agent/
3	((antibiot* or antimicrob* or antibiot* or bact*) adj3 resistance).ab,ti.
4	1 or 2 or 3
5	general practice/ or general practitioner/
6	(clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office).ab,ti.
7	emergency ward/
8	Emergency service*.ab,ti.
9	(emergenc* adj3 (hospital* or department* or dept* or unit*1 or ward*1)).ab,ti.
10	("accident and emergency" or "accident & emergency" or a&e).ab,ti.
11	5 or 6 or 7 or 8 or 9 or 10
12	exp bacterial skin disease/
13	soft tissue disease/ or cellulitis/
14	exp respiratory tract infection/ or exp respiratory tract inflammation/ or exp otitis media/
15	exp urinary tract infection/
16	12 or 13 or 14 or 15
17	4 and 11 and 16

18	(exp animals/ or nonhuman/) not human/
19	17 not 18

C. Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2016

1	MeSH descriptor: [Drug Resistance, Bacterial] explode all trees
2	((antibiot* or antimicrob* or anti-biot* or bact*) near resistance):ti,ab,kw (Word variations have been searched)
3	#1 or #2
4	clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office:ti,ab,kw (Word variations have been searched)
5	Emergency service*:ti,ab,kw (Word variations have been searched)
6	(emergenc* near (hospital* or department* or dept or depts or unit or units or ward or wards)):ti,ab,kw (Word variations have been searched)
7	("accident and emergency" or "accident & emergency" or a&e):ti,ab,kw (Word variations have been searched)
8	#4 or #5 or #6 or #7
9	MeSH descriptor: [Cellulitis] explode all trees
10	MeSH descriptor: [Skin Diseases, Bacterial] explode all trees
11	MeSH descriptor: [Soft Tissue Infections] explode all trees
12	MeSH descriptor: [Respiratory Tract Infections] explode all trees
13	MeSH descriptor: [Urinary Tract Infections] explode all trees
14	(cellulitis or dermatitis or ((skin or cutaneous) near infect*)):ti,ab,kw (Word variations have been searched)
15	((((resp* or chest) near infect*) or "common cold" or sinusitis or rhinosinusitis or rhinitis or "sore throat*" or pharyngitis or nasopharyngitis or tonsillitis or laryngitis or bronchiolitis or bronchitis or pneumonia or "otitis media"):ti,ab,kw (Word variations have been searched)
16	((urin* near infect*) or cystitis):ti,ab,kw (Word variations have been searched)
17	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
18	#3 and #8 and #17

D. Science Citation Index & Conference Proceedings Citation Index (Web of Science): 1945-15 April 2016

1	TOPIC: (((antibiotic* OR anti-biotic* OR antimicrobial* OR bacterial) NEAR/3 resistance)) OR TITLE: (((antibiotic* OR anti-biotic* OR antimicrobial* OR bacterial) AND resistance))
2	TOPIC: (clinic or clinics or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre OR centres or center or centers or office*) OR TOPIC: (emergency)
3	TOPIC: ((respiratory OR chest) NEAR/2 infection*) OR TOPIC: (URTI OR LRTI)
4	TOPIC: (cough* OR "common cold" OR "sore throat*" OR pharyngitis OR nasopharyngitis OR laryngitis OR tonsillitis OR sinusitis OR rhinosinusitis OR rhinitis) OR TOPIC: ("otitis media") OR TOPIC: (bronchiolitis OR bronchitis OR pneumonia)

5	TOPIC: (cellulitis OR dermatitis OR (skin NEAR/3 infect*))
6	TOPIC: (cystitis OR (urin* NEAR/3 infect*))
7	#6 OR #5 OR #4 OR #3
8	#7 AND #2 AND #1

E. Pubmed (<http://www.pubmed.gov>): inception to 15 April 2016

15	Search ((((((clinic[tw] OR clinics[tw] OR practi*[tw] or primary[tw] or physician*[tw] or refer*[tw] or visit*[tw] or outpatient* or consult* or family[tw] or communit*[tw] or ambulatory[tw] or centre[tw] or centres[tw] or center[tw] or centers[tw] or office[tw] OR emergency[tw])) AND (((cellulitis[tw] OR skin infection*[tw] OR dermatitis[tw])) OR (urine infection*[tw] OR urinary infection*[tw] OR urinary tract infection*[tw] OR cystitis[tw])) OR (respiratory infetion*[tw] OR chest infection*[tw] OR respiratory tract infection*[tw] OR "common cold"[tw] OR "sore throat"[tw] OR cough[tw] OR pharyngitis[tw] OR nasopharyngitis[tw] OR sinusitis[tw] OR rhinosinusitis[tw] OR rhinitis[tw] OR tonsillitis[tw] OR laryngitis[tw] OR bronchiolitis[tw] OR bronchitis[tw] OR pneumonia[tw]))) AND (((antibiotic*[ti] OR anti-biotic*[ti] OR antimicrob*[ti] OR bacter*[ti]) AND resistance[ti])) OR ("antibiotic resistance"[tw] OR "anti-biotic resistance"[tw] OR "antimicrobial resistance"[tw] OR "bacterial resistance"[tw]))) AND (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])
14	Search pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]
13	Search (((clinic[tw] OR clinics[tw] OR practi*[tw] or primary[tw] or physician*[tw] or refer*[tw] or visit*[tw] or outpatient* or consult* or family[tw] or communit*[tw] or ambulatory[tw] or centre[tw] or centres[tw] or center[tw] or centers[tw] or office[tw] OR emergency[tw])) AND (((cellulitis[tw] OR skin infection*[tw] OR dermatitis[tw])) OR (urine infection*[tw] OR urinary infection*[tw] OR urinary tract infection*[tw] OR cystitis[tw])) OR (respiratory infetion*[tw] OR chest infection*[tw] OR respiratory tract infection*[tw] OR "common cold"[tw] OR "sore throat"[tw] OR cough[tw] OR pharyngitis[tw] OR nasopharyngitis[tw] OR sinusitis[tw] OR rhinosinusitis[tw] OR rhinitis[tw] OR tonsillitis[tw] OR laryngitis[tw] OR bronchiolitis[tw] OR bronchitis[tw] OR pneumonia[tw]))) AND (((antibiotic*[ti] OR anti-biotic*[ti] OR antimicrob*[ti] OR bacter*[ti]) AND resistance[ti])) OR ("antibiotic resistance"[tw] OR "anti-biotic resistance"[tw] OR "antimicrobial resistance"[tw] OR "bacterial resistance"[tw]))
12	Search (((cellulitis[tw] OR skin infection*[tw] OR dermatitis[tw])) OR (urine infection*[tw] OR urinary infection*[tw] OR urinary tract infection*[tw] OR cystitis[tw])) OR (respiratory infetion*[tw] OR chest infection*[tw] OR respiratory tract infection*[tw] OR "common cold"[tw] OR "sore throat"[tw] OR cough[tw] OR pharyngitis[tw] OR nasopharyngitis[tw] OR sinusitis[tw] OR rhinosinusitis[tw] OR rhinitis[tw] OR tonsillitis[tw] OR laryngitis[tw] OR bronchiolitis[tw] OR bronchitis[tw] OR pneumonia[tw]))
11	Search respiratory infetion*[tw] OR chest infection*[tw] OR respiratory tract infection*[tw] OR "common cold"[tw] OR "sore throat"[tw] OR cough[tw] OR pharyngitis[tw] OR nasopharyngitis[tw] OR sinusitis[tw] OR rhinosinusitis[tw] OR rhinitis[tw] OR tonsillitis[tw] OR laryngitis[tw] OR bronchiolitis[tw] OR bronchitis[tw] OR pneumonia[tw]
10	Search urine infection*[tw] OR urinary infection*[tw] OR urinary tract infection*[tw] OR cystitis[tw]
9	Search cellulitis[tw] OR skin infection*[tw] OR dermatitis[tw]
8	Search clinic[tw] OR clinics[tw] OR practi*[tw] or primary[tw] or physician*[tw] or refer*[tw] or visit*[tw] or outpatient* or consult* or family[tw] or communit*[tw] or ambulatory[tw] or centre[tw] or centres[tw] or center[tw] or centers[tw] or office[tw] OR emergency[tw]

7	Search (((antibiotic*[ti] OR anti-biotic*[ti] OR antimicrob*[ti] OR bacter*[ti]) AND resistance[ti])) OR ("antibiotic resistance"[tw] OR "anti-biotic resistance"[tw] OR "antimicrobial resistance"[tw] OR "bacterial resistance"[tw])
6	Search "antibiotic resistance"[tw] OR "anti-biotic resistance"[tw] OR "antimicrobial resistance"[tw] OR "bacterial resistance"[tw]
5	Search (antibiotic*[ti] OR anti-biotic*[ti] OR antimicrob*[ti] OR bacter*[ti]) AND resistance[ti]

APPENDIX 3 – Risk of bias assessment tool and coding criteria for included randomised controlled studies modelled on the Cochrane Collaboration’s tool for assessing risk of bias in randomised trials

Item	Low risk of bias	High risk of bias	Unclear risk of bias
BIAS DOMAIN 1: SELECTION BIAS			
Patient selection (random sequence generation)	Not applicable*		
Allocation concealment	Not applicable*		
BIAS DOMAIN 2: PERFORMANCE BIAS			
Blinded participants and researchers	Not applicable*		
BIAS DOMAIN 3: DETECTION BIAS			
Blinded outcome assessment	Measures were adequately described to assess outcome blinded to knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive.	Detection bias due to knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive.	Insufficient detail to determine whether outcome assessment was blinded.
BIAS DOMAIN 4: ATTRITION BIAS			
Completeness of outcome data	All patients who entered the trial were adequately accounted for at its conclusion.	There were systematic differences between groups in withdrawals from the study or due to the amount, nature, or handling of incomplete outcome data	Insufficient detail to determine the completeness of outcome data.
BIAS DOMAIN 5: REPORTING BIAS			
Selective reporting	All clinically important outcomes were considered and reported.	There were systematic differences between reported and unreported findings.	Insufficient detail on reported outcomes.
OTHER BIAS	Did authors address any confounders?		
APPLICABILITY	❖ Is there a concern that the included patients do not match the review question? ❖ Is there concern that outcome measure(s) does not match the review question? ❖ Is there concern that the intervention given does not match the review question?		

* As randomisation was not stratified according to antibiotic resistance for RCTs, certain elements of the risk of bias assessment tool for RCTs did not apply to our research question (generation of randomisation sequence, allocation concealment, blinding of treatment allocation).

Risk of bias assessment of included randomised controlled studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Applicability
Barry et al. (1994)	-	-	-	x	✓	✓	?	✓
Buchanan et al. (2005)	-	-	-	x	?	✓	?	✓
Dagan et al (1992)	-	-	-	✓	✓	✓	✓	✓
Dagan et al. (1996)	-	-	-	x	✓	✓	?	✓
Giordano et al. (2006)	-	-	-	x	?	✓	?	✓
Gupta, et al. (2007)	-	-	-	x	?	✓	?	✓
Hagberg, et al. (2003)	-	-	-	x	?	✓	?	✓
Hoberman et al. (2005)	-	-	-	x	✓	✓	?	✓
O'Doherty et al. (1997)	-	-	-	x	✓	✓	?	✓
Quinn et al. (2003)	-	-	-	x	✓	✓	?	✓
van Merode et al. (2005)	-	-	-	x	✓	✓	?	✓
van Rensburg et al.(2005)	-	-	-	x	x	?	?	✓
Zhanel et al. (2014)	-	-	-	x	✓	✓	?	✓

✓ Low risk of bias; x High risk of bias; ? Unclear risk of bias; - Not applicable

APPENDIX 4 – Risk of bias assessment tool and coding criteria for included observational studies based on CASP (Critical Appraisal Skills Programme) checklist for cohort studies

Item	Low risk of bias	High risk of bias	Unclear risk of bias
Research question	Research question or objective was stated clearly	Research question or objective was not reported.	Insufficient information to discern objective of the study
Characteristics of study population	The study population was clearly specified and defined.	The study population was not reported.	Insufficient information to discern study population
Representative study population	Cohort of exposed and unexposed drawn for same population or administrative database of patients presenting at same points of care over the same time frame	Exposed and unexposed participants presenting to different points of care or over a different time frame or with very specific bacterial subspecies	Insufficient information to determine whether the study population was representative of the defined population
Measurement of antibiotic exposure	The exposure was accurately measured to minimise bias e.g. secure records, pharmacy records or repeated interview asking about current use/exposure	Exposure was measured following interview at a single point in time; self-reported exposure or individuals who are asked to retrospectively confirm their exposure status.	Insufficient information to determine how exposure information was obtained.
Outcome of interest ("clinical response failure")	The outcome of interest was not present at the start of the study.	The outcome of interest was present at the start of the study	Insufficient information to judge whether participants had the outcome of interest at the start of the study.
Confounding or matching (case control)	Comprehensive matching or adjustment for all plausible prognostic variables.	Matching or adjustment for a minority of plausible prognostic variables, or no matching or adjustment at all.	Insufficient information to determine whether matching or adjustment was performed.
Measurement of outcome	The outcome of accurately measured e.g. independent blind assessment or record linkage;	The outcome was assessed unblinded or self-reported.	Insufficient information given.
Follow-up	No missing outcome data or missing data unlikely to be related to true outcome. There was a sufficient timeframe to see an association between exposure and outcome. Or loss to follow-up after baseline 20% or less?	Missing outcome data likely to be related to true outcome (imbalance in numbers or reasons for missing data across intervention groups). Different length of follow-up periods across study groups.	Insufficient information about follow-up
Blinding of outcome	The outcome assessors were blinded to the	There were systematic differences between	Insufficient detail to determine whether outcome

assessment	exposure status of participants.	groups in how outcomes are determined.	assessment was blinded.
Was loss to follow-up after baseline 20% or less?	There were < 20% loss of participants at follow-up	More than 20% loss of participants at follow-up	Insufficient detail to determine.

Risk of bias assessment of included observational studies

	Brown et al. (2002)	Butler et al. (2006)	Cao et al. (2010)	Hoberman et al. (1996)	Kawai et al. (2012)	Little et al. (2010)	McNulty et al. (2006)	Noskin et al. (2001)	Raz et al. (2002)	Seppala et al. (2002)	Soraas et al. (2014)	Vallano et al. (2006)	Yanagihara et al. (2004)
Was the research question or objective clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the study population clearly specified and defined?	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓
Was the cohort representative of the defined population?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓
Was the exposure accurately measured to minimise bias?	?	✓	✓	?	?	✓	✓	✓	✓	✓	✓	✓	✓
Was the outcome of interest present at the start of the study?	✓	?	✓	✓	✓	✓	✓	✓	✓	?	✓	?	?
Did the authors attempt to identify all important confounding factors or take account of these in the design and/or analysis?	✓	✓	x	x	✓	✓	✓	x	x	x	✓	x	x
Was the outcome accurately measured to minimise bias?	✓	✓	✓	✓	?	?	?	x	?	x	✓	?	✓
Was the follow up of cohorts adequate?	✓	✓	✓	✓	x	✓	✓	?	✓	-	✓	✓	-
Were the outcome assessors blinded to the exposure status of participants?	✓	✓	?	x	x	x	?	x	x	x	?	?	x
Was loss to follow-up after baseline 20% or less?	✓	?	?	✓	x	?	?	?	?	-	?	✓	-

✓ Low risk of bias; x High risk of bias; ? Unclear risk of bias; - Not applicable

APPENDIX 5 – Diagnostic approach of significant bacterial infection in *E. coli* urinary tract infections

Study	Clinical criteria for diagnosis of urinary tract infections	Laboratory criteria for diagnosis of significant bacterial infection	Antimicrobial susceptibility testing	Mixed infections
Brown et al. 2002	SD	$\geq 10^3$ CFU/ ml	NR	NR
Butler et al. 2006	Clinically suspected UTI	$> 10^5$ CFU/ ml	BSAC‡	Mixed infections were included if <i>E. coli</i> (71%) was reported
Gupta et al. 2007	S	$\geq 10^2$ CFU/mL of uropathogen	CLSI/NCCLS*	<i>E. coli</i> alone (82%) or in combination with another uropathogen (4%).
van Merode et al. 2005	S	NR	SWAB standard†	<i>E. coli</i> (65%) Mixed uropathogens
McNulty et al. 2006	SD [§]	$\geq 10^4$ CFU/mL of all organisms	BSAC‡	Pure coliform (89%) Mixed uropathogens
Noskin et al. 2001	SD	$\geq 10^4$ cfu/ml) with no more than 2 bacteria	NCCLS*	<i>E. coli</i> alone (74%) or in combination with another uropathogen (4%)
Raz et al. 2002	SD	NR	NCCLS*	<i>E. coli</i> (78%) Mixed uropathogens
Soraas et al. 2014	NR	$> 10^4$ CFU/ml of uropathogen ^a	EUCAST±	No, ESBL- <i>E. coli</i> non-ESBL- <i>E. coli</i> only
Vallano et al. 2006	NR	NR	NCCLS*	<i>E. coli</i> (75%) Mixed uropathogens

S: symptoms only; SD: symptoms and urine dipstick; NR: not reported; * Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards; †SWAB.nl (Stichting Werkgroep Antibioticabeleid); § Over the first 18 months of the study, clinicians used urine dipstick; ‡BSAC: British Society for Antimicrobial Chemotherapy; a: ESBL *E.coli* ; ± EUCAST: The European Committee on Antimicrobial Susceptibility Testing

APPENDIX 6 – Diagnostic approach of significant bacterial infection in *S. pneumoniae* community-acquired pneumonia

Study	Clinical criteria for diagnosis of community-acquired pneumonia	Laboratory criteria for diagnosis of significant bacterial infection	Antimicrobial susceptibility testing
Hagberg et al. 2003	S, R	L	NCCLS
O'Doherty et al. 1997	S, R	L	NCCLS
van Rensburg et al. 2005	S	L	NCCLS
Yanagihara et al. 2004	S, R	L	NR
Zhanel et al. 2014	NR	NR	CLSI/NCCLS*

S: Symptoms; R: radiographic evidence; L: peripheral blood (WCC) count and/or Gram-positive diplococci; NCCLS: National Committee for Clinical Laboratory Standards; NR: not reported; * Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards).

APPENDIX 7 – Diagnostic approach of significant bacterial infection in *S. pneumoniae* acute otitis media

Study	Clinical criteria for diagnosis of acute otitis media	Laboratory criteria for diagnosis of significant bacterial infection	Antimicrobial susceptibility testing
Barry et al. 1994	S, E, T	Culture	"Bacterial isolates were identified by standard methods"
Dagan et al. 1996	S, E, T	Culture	NCCLS
Hoberman et al. 1996	S,E,T	Culture	NCCLS
Hoberman et al. 2005	S, E, T	Culture	NCCLS
Zhanel et al. 2014	NR	NR	CLSI/NCCLS*

S: Symptoms; E: Examination; T: tympanocentesis or ear swab; NR: not reported; NCCLS: National Committee for Clinical Laboratory Standards; * Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards).

APPENDIX 8 – Unadjusted odds ratios for clinical response failure between antibiotic-resistant and antibiotic-sensitive Group A *β*-haemolytic streptococcus sore throat

Study	<i>n</i> ^a	Treatment antibiotic arm	No. of failures/total resistant group ^c	No. of failures/total sensitive group ^d	Unadjusted OR [95% CI]
Quinn et al. 2003	187 isolates	Telithromycin	1/5	10/145	3.38 [0.34–33.11]
Quinn et al. 2003	173 isolates	Clarithromycin	2/4	10/131	12.10 [1.54–95.25]
Seppala et al. 2002	196	Erythromycin	9/19	1/26	22.50 [2.51–201.50]
Seppala et al. 2002	333	Penicillin	5/57 ^b	6/171 ^b	6.93 [1.02–47.23]

a: Total number of patients with GABHS unless indicated. b: numbers based on erythromycin-susceptibility. c: Total number of participants with antibiotic-resistant infections. d: Total number of participants with antibiotic-sensitive infections. OR: odds ratio. CI: confidence interval

APPENDIX 9 – Unadjusted odds ratios for clinical response failure between antibiotic-resistant and antibiotic-sensitive *S. pneumoniae* acute maxillary sinusitis

Study	<i>n</i> ^a	Treatment antibiotic arm	No. of failures/total resistant group ^c	No. of failures/total sensitive group ^d	Unadjusted OR [95% CI]
Buchanan et al. 2005 ^b	126	Telithromycin	0/1	9/77	2.40 [0.09–63.35]
Zhanel et al. 2014	57	Azithromycin	2/19	0/38	11.00 [0.50–241.38]

a: Total number of patients with *S.pneumoniae*. b: Buchanan et al. also report outcomes for *H. influenzae*. c: Total number of participants with antibiotic-resistant infections. d: Total number of participants with antibiotic-sensitive infections. OR: odds ratio. CI: confidence interval

APPENDIX 10 – Unadjusted odds ratios for clinical response failure between antibiotic-resistant and antibiotic-sensitive *S. aureus* skin infection

Study	<i>n</i> ^a	Treatment antibiotic arm	No. of failures/total resistant group ^e	No. of failures/total sensitive group ^f	Unadjusted OR [95% CI]
Dagan et al. 1992 ^b	43	Erythromycin	8/17	2/26	10·67 [1·89–60·08]
Dagan et al. 1992 ^b	46	Mupirocin	0/10	1/36	1·13 [0·04–29·77]
Giordano et al. 2006 ^c	78	Cefdinir	3/38 ^d	3/40	1·06 [0·20–5·59]
Giordano et al. 2006 ^c	73	Cephalexin	4/41 ^d	3/29	1·05 [0·22–5·04]

a: Total number of evaluable patients with *S. aureus* where resistance and outcome data available. b: impetigo; c: Uncomplicated skin and skin structure infections (USSSI) such as impetigo, erysipelas, cellulitis, folliculitis, furunculosis, wound infection, and simple abscesses; d: isolates of *S. aureus* were tested for susceptibility to oxacillin. e: Total number of participants with antibiotic resistant infections. f: Total number of participants with antibiotic-sensitive infections. OR: odds ratio. CI: confidence interval

APPENDIX 11 – Unadjusted odds ratios for “patient re-consultation” between antibiotic-resistant and antibiotic-sensitive *E. coli* urinary tract infections

Study	Total ^a	Follow-up period	Infection type	Treatment antibiotic	Unadjusted OR [95% CI]	Re-consultations /total resistant group ^b	Re-consultations /total sensitive group ^c
Brown et al. 2002	104	14 days	<i>E. coli</i>	TMP-SMX*	18.89 [4.93-72.43]	15/33	3/71
Butler et al. 2006	862	30 days	<i>E. coli</i>	Empiric**	2.75 [1.81-4.18]	55/103	223/759
McNulty et al. 2006	317	30 days	<i>E. coli</i>	Trimethoprim	4.72 [2.39-9.31]	20/44	41/273

a: Total number of participants where resistance and outcomes data available. b: Total number of participants with antibiotic-resistant infections. c: Total number of participants with antibiotic-sensitive infection. *TMP-SMX Trimethoprim-sulfamethoxazole. ** resistant to prescribed antibiotic. OR: odds ratio. CI: confidence interval

APPENDIX 12 – Unadjusted odds ratios for “further antibiotic prescription” between antibiotic-resistant and antibiotic-sensitive infections

Study	Total ^a	Time period	Infection type	Treatment antibiotic	Unadjusted OR [95% CI]	Further antibiotic prescriptions /total resistant group ^b	Further antibiotic prescriptions /total sensitive group ^c
Cao et al. 2010	59	48-72 hours	<i>M. pneumoniae</i> CAP	Empiric**	1.67 [0.52-5.34]	20/42	6/17
Butler et al. 2006	816	30 days	<i>E. coli</i> UTI	Empiric*	2.30 [1.69-3.13]	141/391	92/467
Kawai et al. 2012	30	48-72 hours	<i>M. pneumoniae</i> CAP	Macrolides	100.43 [4.69-2,152]	18/21	0/9
Soraas et al. 2014	343	14 days	ESBL- <i>E. coli</i> UTI	Mecillinam	3.98 [1.70-6.73]	43/81	58/262

a: Total number of participants where resistance and outcomes data available. b: Total number of participants with antibiotic-resistant infections. c: Total number of participants with antibiotic-sensitive infections. ** resistant to erythromycin. *resistant to prescribed antibiotic. OR: odds ratio. CI: confidence interval

APPENDIX 13 – CPRD diagnostic codes for acute respiratory tract infections (RTI)

Medcode	Read Code	Read Term
Bronchitis		
43362	H060700	Acute streptococcal bronchitis
4519	14B3.11	H/O: bronchitis
29669	H06.00	Acute bronchitis and bronchiolitis
5978	H060.11	Acute wheezy bronchitis
50396	H060000	Acute fibrinous bronchitis
101775	H060100	Acute membranous bronchitis
71370	H060200	Acute pseudomembranous bronchitis
11072	H060300	Acute purulent bronchitis
21145	H060400	Acute croupous bronchitis
11101	H060500	Acute tracheobronchitis
9043	H060600	Acute pneumococcal bronchitis
21492	H060800	Acute haemophilus influenzae bronchitis
49794	H060900	Acute neisseria catarrhalis bronchitis
31886	H060A00	Acute bronchitis due to mycoplasma pneumoniae
93153	H060B00	Acute bronchitis due to coxsackievirus
29273	H060C00	Acute bronchitis due to parainfluenza virus
48593	H060D00	Acute bronchitis due to respiratory syncytial virus
64890	H060E00	Acute bronchitis due to rhinovirus
65916	H060F00	Acute bronchitis due to echovirus
55391	H060v00	Subacute bronchitis unspecified
1382	H060w00	Acute viral bronchitis unspecified
24800	H060x00	Acute bacterial bronchitis unspecified
20198	H060z00	Acute bronchitis NOS
1019	H061.00	Acute bronchiolitis
54533	H061000	Acute capillary bronchiolitis
41589	H061100	Acute obliterating bronchiolitis
17185	H061200	Acute bronchiolitis with bronchospasm
69192	H061300	Acute exudative bronchiolitis
18451	H061500	Acute bronchiolitis due to respiratory syncytial virus
66228	H061600	Acute bronchiolitis due to other specified organisms
17917	H061z00	Acute bronchiolitis NOS
41137	H06z.00	Acute bronchitis or bronchiolitis NOS
148	H30.00	Bronchitis unspecified
3163	H300.00	Tracheobronchitis NOS
3480	H30z.00	Bronchitis NOS
73100	Hyu1000	[X]Acute bronchitis due to other specified organisms
99214	Hyu1100	[X]Acute bronchiolitis due to other specified organisms
8025	H0...00	Acute respiratory infections
368	H00.11	Common cold
1246	H00.12	Coryza - acute
6620	H00.13	Febrile cold
896	H00.14	Nasal catarrh - acute
9093	H00.15	Pyrexial cold
3821	H00.16	Rhinitis - acute
26010	H05.00	Other acute upper respiratory infections
6294	H051.00	Acute upper respiratory tract infection
4221	H054.00	Recurrent upper respiratory tract infection
15628	H05y.00	Other upper respiratory infections of multiple sites
76	H05z.00	Upper respiratory infection NOS
2637	H05z.11	Upper respiratory tract infection NOS
6421	H05z.12	Viral upper respiratory tract infection NOS

293	H06z111	Respiratory tract infection
2476	H07.00	Chest cold
23640	H0y.00	Other specified acute respiratory infections
21113	H0z.00	Acute respiratory infection NOS
Cough		
4931	1712	Dry cough
104163	R062100	[D]Episodic dry cough
3645	1716.11	Coughing up phlegm
292	1719	Chesty cough
1025	1719.11	Bronchial cough
7773	1714	Productive cough -green sputum
3628	171B.00	Persistent cough
29318	171D.00	Evening cough
92	171..00	Cough
3068	1717	Night cough present
7706	1713	Productive cough -clear sputum
4836	173B.00	Nocturnal cough / wheeze
1273	171..11	C/O - cough
7707	171Z.00	Cough symptom NOS
1160	R062.00	[D]Cough
1234	1716	Productive cough NOS
4070	171C.00	Morning cough
7708	1715	Productive cough-yellow sputum
43795	171E.00	Unexplained cough
18907	171F.00	Cough with fever
26211	171G.00	Bovine cough
22318	171H.00	Difficulty in coughing up sputum
19470	171J.00	Reflux cough
90332	171K.00	Barking cough
Otitis Media		
24082	2D94.00	O/E - tympanic membrane pink
18363	2D95.00	O/E - tympanic membrane red
24798	2D96.00	O/E -tympanic membrane bulging
5813	1C3..00	Earache symptoms
5831	1C32.00	Unilateral earache
6657	1C33.00	Bilateral earache
16508	1C3Z.00	Earache symptom NOS
5903	A552.00	Postmeasles otitis media
5577	F51.00	Nonsuppurative otitis media + eustachian tube disorders
5887	F510.00	Acute non suppurative otitis media
18371	F510000	Acute otitis media with effusion
5148	F510011	Acute secretory otitis media
7730	F510100	Acute serous otitis media
21012	F510200	Acute mucoid otitis media
15973	F510300	Acute sanguinous otitis media
20374	F510z00	Acute nonsuppurative otitis media NOS
17772	F514.00	Unspecified nonsuppurative otitis media
5102	F514100	Serous otitis media NOS
5390	F514200	Catarrhal otitis media NOS
21749	F514300	Mucoid otitis media NOS
21725	F514z00	Nonsuppurative otitis media NOS
1474	F52.00	Suppurative and unspecified otitis media
2137	F520.00	Acute suppurative otitis media
10781	F520000	Acute suppurative otitis media tympanic membrane intact
20669	F520100	Acute suppurative otitis media tympanic membrane ruptured
61497	F520300	Acute suppurative otitis media due to disease EC

20372	F520z00	Acute suppurative otitis media NOS
15568	F524.00	Purulent otitis media NOS
20871	F524000	Bilateral suppurative otitis media
9973	F525.00	Recurrent acute otitis media
3694	F526.00	Acute left otitis media
4348	F527.00	Acute right otitis media
1134	F528.00	Acute bilateral otitis media
267	F52z.00	Otitis media NOS
1513	F52z.11	Infection ear
99403	FyuP000	[X]Other acute nonsuppurative otitis media
98656	FyuP300	[X]Otitis media in bacterial diseases classified elsewhere
72916	FyuP400	[X]Otitis media in viral diseases classified elsewhere
72914	FyuP500	[X]Otitis media in other diseases classified elsewhere
46709	SN30.11	Aero-otitis media
Sinusitis		
980	H01.00	Acute sinusitis
243	H01.11	Sinusitis
94218	H014.00	Acute rhinosinusitis
7021	H010.00	Acute maxillary sinusitis
18555	H010.11	Antritis - acute
8213	H011.00	Acute frontal sinusitis
15724	H012.00	Acute ethmoidal sinusitis
38816	H013.00	Acute sphenoidal sinusitis
29696	H01y.00	Other acute sinusitis
19284	H01y000	Acute pansinusitis
60733	H01yz00	Other acute sinusitis NOS
33664	H01z.00	Acute sinusitis NOS
3624	H130.12	Maxillary sinusitis
2984	H131.11	Frontal sinusitis
17173	H135.00	Recurrent sinusitis
2233	H13y100	Pansinusitis
97330	Hyu0000	[X]Other acute sinusitis
73094	SN31.11	Aerosinusitis
Sore throat-tonsillitis		
16718	A340100	Streptococcal laryngitis
16067	AA1z.11	Vincent's laryngitis
41324	H04.00	Acute laryngitis and tracheitis
142	H040.00	Acute laryngitis
26038	H040000	Acute oedematous laryngitis
62885	H040100	Acute ulcerative laryngitis
10765	H040200	Acute catarrhal laryngitis
31501	H040300	Acute phlegmonous laryngitis
43317	H040400	Acute haemophilus influenzae laryngitis
51562	H040600	Acute suppurative laryngitis
5115	H040w00	Acute viral laryngitis unspecified
52756	H040x00	Acute bacterial laryngitis unspecified
22720	H040z00	Acute laryngitis NOS
1257	H041.00	Acute tracheitis
12476	H041000	Acute tracheitis without obstruction
68867	H041100	Acute tracheitis with obstruction
16313	H041z00	Acute tracheitis NOS
10087	H042.00	Acute laryngotracheitis
1285	H042.11	Laryngotracheitis
25259	H042000	Acute laryngotracheitis without obstruction
69898	H042100	Acute laryngotracheitis with obstruction
24471	H042z00	Acute laryngotracheitis NOS

10641	H043.00	Acute epiglottitis (non strep)
69489	H043.11	Viral epiglottitis
65650	H043000	Acute epiglottitis without obstruction
48669	H043100	Acute epiglottitis with obstruction
38128	H043200	Acute obstructive laryngitis
19431	H043211	Croup
892	H043z00	Acute epiglottitis NOS
1142	H044.00	Croup
16120	H04z.00	Acute laryngitis and tracheitis NOS
21415	H052.00	Pharyngotracheitis
4718	H055.00	Pharyngolaryngitis
15774	H271000	Influenza with laryngitis
1934	H301.00	Laryngotracheobronchitis
5755	1C9.00	Sore throat symptom
404	1C9.11	Throat soreness
5553	1C92.00	Has a sore throat
12489	1C93.00	Persistent sore throat
15287	1C9Z.00	Sore throat symptom NOS
386	1CB3.00	Throat pain
15039	R041.00	[D]Throat pain
7366	1CB3.11	Pain in throat
24788	2DC2.00	O/E - granular pharyngitis
14931	2DC3.00	Inflamed throat
54777	A34.00	Streptococcal sore throat and scarlatina
1765	A340.00	Streptococcal sore throat
4902	A340200	Streptococcal pharyngitis
16217	A340z00	Streptococcal sore throat NOS
16184	A34z.00	Streptococcal sore throat with scarlatina NOS
31536	AA12.00	Vincent's pharyngitis
53708	AA25.11	Rhinopharyngitis mutilans
3260	H00.00	Acute nasopharyngitis
893	H02.00	Acute pharyngitis
6014	H02. 11	Sore throat NOS
6466	H02.12	Viral sore throat NOS
310	H02.13	Throat infection - pharyngitis
36219	H020.00	Acute gangrenous pharyngitis
24708	H021.00	Acute phlegmonous pharyngitis
21486	H022.00	Acute ulcerative pharyngitis
17899	H023.00	Acute bacterial pharyngitis
92428	H023000	Acute pneumococcal pharyngitis
29589	H023100	Acute staphylococcal pharyngitis
53395	H023z00	Acute bacterial pharyngitis NOS
4868	H024.00	Acute viral pharyngitis
407	H02z.00	Acute pharyngitis NOS
18908	H050.00	Acute laryngopharyngitis
10093	H053.00	Tracheopharyngitis
38879	H121100	Atrophic pharyngitis
21562	H121200	Granular pharyngitis
15794	H121300	Hypertrophic pharyngitis
56361	H121400	Pharyngitis keratosa
29617	H271100	Influenza with pharyngitis
8480	J083600	Uvulitis
93964	Hyu0100	[X]Acute pharyngitis due to other specified organisms
7266	2DB6.00	O/E - follicular tonsillitis
8496	A340300	Streptococcal tonsillitis
58538	A383000	Fusobacterial necrotising tonsillitis
16954	AA1z.12	Vincent's tonsillitis
138	H03.00	Acute tonsillitis

11499	H03.11	Throat infection - tonsillitis
2125	H03.12	Tonsillitis
12010	H030.00	Acute erythematous tonsillitis
4061	H031.00	Acute follicular tonsillitis
8452	H032.00	Acute ulcerative tonsillitis
37409	H033.00	Acute catarrhal tonsillitis
59986	H034.00	Acute gangrenous tonsillitis
10156	H035.00	Acute bacterial tonsillitis
58188	H035000	Acute pneumococcal tonsillitis
64973	H035100	Acute staphylococcal tonsillitis
15970	H035z00	Acute bacterial tonsillitis NOS
9357	H036.00	Acute viral tonsillitis
1747	H037.00	Recurrent acute tonsillitis
20104	H03z.00	Acute tonsillitis NOS
35249	H14y600	Lingual tonsillitis
73118	Hyu0200	[X]Acute tonsillitis due to other specified organisms

APPENDIX 14 – CPRD product codes for relevant antibiotics used in the treatment of acute “respiratory tract infections” as listed in the British National Formulary (BNF) for Children Chapter 5.1

Product Code	Product Name	Drug substance name	BNF header
Cephalosporin			
10455	Keflex 250mg/5ml Liquid (Eli Lilly and Company Ltd)	Cefalexin	Cephalosporins
5859	Ceporex 500mg/5ml Oral solution (Galen Ltd)	Cefalexin	Cephalosporins
27017	Kiflone 500mg Capsule (Berk Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
9520	Cefaclor 250mg Capsule (Lagap)	Cefaclor monohydrate	Cephalosporins
44299	Cefradine 250mg capsules (Kent Pharmaceuticals Ltd)	Cefradine	Cephalosporins
32642	Cefalexin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
34253	Cefalexin 250mg capsules (A A H Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
55211	Cefaclor 500mg capsules (Kent Pharmaceuticals Ltd)	Cefaclor monohydrate	Cephalosporins
2661	Ceporex 500mg Capsule (Galen Ltd)	Cefalexin	Cephalosporins
30769	Cefradine 250mg capsules (IVAX Pharmaceuticals UK Ltd)	Cefradine	Cephalosporins
26989	Kiflone 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
29202	Cefalexin 500mg tablets (A A H Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
47983	Cefuroxime 250mg tablets (A A H Pharmaceuticals Ltd)	Cefuroxime axetil	Cephalosporins
61661	Cefalexin 125mg/5ml oral suspension (Waymade Healthcare Plc)	Cefalexin	Cephalosporins
26233	Keftid 125mg/5ml oral suspension (Co-Pharma Ltd)	Cefaclor monohydrate	Cephalosporins
47993	Cefuroxime (as axetil) 500mg tablets	Cefuroxime Axetil	Cephalosporins
54864	Cefalexin 250mg capsules (Alliance Healthcare (Distribution) Ltd)	Cefalexin	Cephalosporins
41106	Ceporex 125mg/5ml syrup (Co-Pharma Ltd)	Cefalexin	Cephalosporins
19160	Cefalexin 250mg capsules (Generics (UK) Ltd)	Cefalexin	Cephalosporins
43433	Cefradine 250mg capsules (Teva UK Ltd)	Cefradine	Cephalosporins
1384	Cefalexin 125mg/5ml suspension	Cefalexin	Cephalosporins
14607	Cefaclor 125mg/5ml Liquid (Lagap)	Cefaclor monohydrate	Cephalosporins

33802	Cefalexin 250mg Capsule (Berk Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
26236	Keftid 500mg capsules (Co-Pharma Ltd)	Cefaclor monohydrate	Cephalosporins
40914	Ceporex 500mg tablets (Co-Pharma Ltd)	Cefalexin	Cephalosporins
9698	Cefalexin 250mg tablets (Teva UK Ltd)	Cefalexin	Cephalosporins
4576	Distaclor 250mg Capsule (Dista Products Ltd)	Cefaclor monohydrate	Cephalosporins
865	Cefalexin 500mg tablets	Cefalexin	Cephalosporins
32181	Cefalexin 125mg/5ml oral suspension (Actavis UK Ltd)	Cefalexin	Cephalosporins
30772	Cefaclor 250mg capsules (Ranbaxy (UK) Ltd)	Cefaclor monohydrate	Cephalosporins
8085	Ceporex 500mg Tablet (Galen Ltd)	Cefalexin	Cephalosporins
41049	Ceporex 250mg tablets (Co-Pharma Ltd)	Cefalexin	Cephalosporins
52283	Cefalexin 250mg capsules (Arrow Generics Ltd)	Cefalexin	Cephalosporins
58920	Cefuroxime 250mg tablets (Tillomed Laboratories Ltd)	Cefuroxime axetil	Cephalosporins
12850	Cefuroxime 125mg tablets	Cefuroxime axetil	Cephalosporins
9664	Cefalexin 500mg capsules (IVAX Pharmaceuticals UK Ltd)	Cefalexin	Cephalosporins
54955	Cefalexin 500mg capsules (Milpharm Ltd)	Cefalexin	Cephalosporins
19138	Cefalexin 500mg capsules (Actavis UK Ltd)	Cefalexin	Cephalosporins
40884	Ceporex 250mg capsules (Co-Pharma Ltd)	Cefalexin	Cephalosporins
52851	Cefalexin 500mg capsules (Alliance Healthcare (Distribution) Ltd)	Cefalexin	Cephalosporins
11989	Keflex 250mg capsules (Flynn Pharma Ltd)	Cefalexin	Cephalosporins
41853	Keftid 250mg/5ml oral suspension (Co-Pharma Ltd)	Cefaclor monohydrate	Cephalosporins
319	Distaclor 500mg Capsule (Dista Products Ltd)	Cefaclor monohydrate	Cephalosporins
9219	Distaclor 250mg/5ml Liquid (Dista Products Ltd)	Cefaclor monohydrate	Cephalosporins
9157	Keflex 250mg Tablet (Eli Lilly and Company Ltd)	Cefalexin	Cephalosporins
36330	Cefalexin 250mg tablets (Actavis UK Ltd)	Cefalexin	Cephalosporins
17150	Ceporex 125mg/1.25ml Drops (Glaxo Laboratories Ltd)	Cefalexin	Cephalosporins
8625	Ceporex 250mg/5ml Liquid (Galen Ltd)	Cefalexin	Cephalosporins
1306	Suprax 200mg tablets (Sanofi)	Cefixime	Cephalosporins
34913	Cefaclor 125mg/5ml Oral suspension (Genus Pharmaceuticals Ltd)	Cefaclor monohydrate	Cephalosporins
19144	Cefalexin 125mg/5ml oral suspension sugar free (Teva UK Ltd)	Cefalexin	Cephalosporins

1038	Cefaclor 125mg/5ml oral suspension	Cefaclor monohydrate	Cephalosporins
56610	Cefaclor 125mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Cefaclor monohydrate	Cephalosporins
53945	Cefalexin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Cefalexin	Cephalosporins
30610	Nicef 250mg capsules (Co-Pharma Ltd)	Cefradine	Cephalosporins
400	Cefalexin 500mg capsules	Cefalexin	Cephalosporins
2227	Cefalexin 500mg/5ml oral suspension	Cefalexin	Cephalosporins
59068	Cefuroxime 250mg tablets (Teva UK Ltd)	Cefuroxime axetil	Cephalosporins
8019	Ceporex 250mg Tablet (Galen Ltd)	Cefalexin	Cephalosporins
40747	Cefalexin 250mg chewable tablets	Cefalexin	Cephalosporins
24618	Keflex 500mg capsules (Flynn Pharma Ltd)	Cefalexin	Cephalosporins
6651	Cefalexin 125mg/5ml oral suspension sugar free	Cefalexin	Cephalosporins
41736	Cefalexin 250mg capsules (Kent Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
3737	Cefaclor 250mg/5ml oral suspension	Cefaclor monohydrate	Cephalosporins
39417	Cefalexin 125mg/5ml oral suspension (Generics (UK) Ltd)	Cefalexin	Cephalosporins
830	Keflex 250mg tablets (Flynn Pharma Ltd)	Cefalexin	Cephalosporins
9603	Keflex 500mg Tablet (Eli Lilly and Company Ltd)	Cefalexin	Cephalosporins
34629	Cefradine 500mg capsules (Generics (UK) Ltd)	Cefradine	Cephalosporins
7485	Keflex 125mg/5ml Liquid (Eli Lilly and Company Ltd)	Cefalexin	Cephalosporins
47163	Cefalexin 250mg tablets (Arrow Generics Ltd)	Cefalexin	Cephalosporins
34844	Cefradine 500mg capsules (IVAX Pharmaceuticals UK Ltd)	Cefradine	Cephalosporins
33334	Cefalexin 250mg tablets (A A H Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
43425	Cefaclor 500mg capsules (A A H Pharmaceuticals Ltd)	Cefaclor monohydrate	Cephalosporins
46973	Cefaclor 250mg/5ml Oral suspension (Genus Pharmaceuticals Ltd)	Cefaclor monohydrate	Cephalosporins
34543	Cefradine 250mg capsules (A A H Pharmaceuticals Ltd)	Cefradine	Cephalosporins
26207	Keftid 250mg capsules (Co-Pharma Ltd)	Cefaclor monohydrate	Cephalosporins
29748	Cefalexin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
27072	Keflex 125mg/5ml oral suspension (Flynn Pharma Ltd)	Cefalexin	Cephalosporins

52282	Cefalexin 250mg capsules (Milpharm Ltd)	Cefalexin	Cephalosporins
8008	Ceporex 250mg/5ml Oral solution (Galen Ltd)	Cefalexin	Cephalosporins
41968	Cefalexin 250mg/5ml oral suspension (Teva UK Ltd)	Cefalexin	Cephalosporins
41230	Ceporex 500mg/5ml syrup (Co-Pharma Ltd)	Cefalexin	Cephalosporins
7624	Velosef 250mg capsules (Bristol-Myers Squibb Pharmaceuticals Ltd)	Cefradine	Cephalosporins
31827	Cefalexin 500mg tablets (IVAX Pharmaceuticals UK Ltd)	Cefalexin	Cephalosporins
192	Ceporex 250mg Capsule (Galen Ltd)	Cefalexin	Cephalosporins
1693	Cefalexin 125mg/5ml oral suspension	Cefalexin	Cephalosporins
45221	Cefalexin 250mg/5ml oral suspension (Actavis UK Ltd)	Cefalexin	Cephalosporins
39703	Cefaclor 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Cefaclor monohydrate	Cephalosporins
725	Cefuroxime 125mg/5ml oral suspension	Cefuroxime axetil	Cephalosporins
48025	Cefaclor 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Cefaclor monohydrate	Cephalosporins
3678	Cefuroxime 250mg tablets	Cefuroxime axetil	Cephalosporins
56250	Cefadroxil 500mg capsules (Sandoz Ltd)	Cefadroxil monohydrate	Cephalosporins
36578	Cefalexin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Cefalexin	Cephalosporins
33329	Cefalexin 125mg/5ml oral suspension (Teva UK Ltd)	Cefalexin	Cephalosporins
366	Cefaclor 250mg capsules	Cefaclor monohydrate	Cephalosporins
36569	Cefalexin 500mg capsules (Kent Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
10794	Zinnat 125mg tablets (GlaxoSmithKline UK Ltd)	Cefuroxime axetil	Cephalosporins
29281	Cefalexin 500mg capsules (Teva UK Ltd)	Cefalexin	Cephalosporins
31110	Keflex 500mg tablets (Flynn Pharma Ltd)	Cefalexin	Cephalosporins
34965	Cefradine 500mg capsules (A A H Pharmaceuticals Ltd)	Cefradine	Cephalosporins
41192	Cefalexin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Cefalexin	Cephalosporins
59069	Cefalexin 250mg tablets (Phoenix Healthcare Distribution Ltd)	Cefalexin	Cephalosporins
9293	Cefaclor 250mg/5ml oral suspension sugar free	Cefaclor monohydrate	Cephalosporins
34654	Cefradine 500mg capsules (Teva UK Ltd)	Cefradine	Cephalosporins
11992	Baxan 500mg capsules (Bristol-Myers Squibb	Cefadroxil monohydrate	Cephalosporins

	Pharmaceuticals Ltd)		
19152	Cefalexin 250mg capsules (Actavis UK Ltd)	Cefalexin	Cephalosporins
20420	Cefaclor 250mg/5ml Liquid (Generics (UK) Ltd)	Cefaclor monohydrate	Cephalosporins
9690	Cefalexin 250mg capsules (Teva UK Ltd)	Cefalexin	Cephalosporins
4689	Cefaclor 500mg Capsule (Lagap)	Cefaclor monohydrate	Cephalosporins
843	Cefixime 200mg tablets	Cefixime	Cephalosporins
12276	Keflex 500mg Capsule (Eli Lilly and Company Ltd)	Cefalexin	Cephalosporins
25384	Distaclor 125mg/5ml oral suspension (Flynn Pharma Ltd)	Cefaclor monohydrate	Cephalosporins
52179	Cefadroxil 500mg capsules (Phoenix Healthcare Distribution Ltd)	Cefadroxil monohydrate	Cephalosporins
6671	Cefalexin 250mg/5ml oral suspension sugar free	Cefalexin	Cephalosporins
20409	Cefaclor 250mg/5ml Liquid (Lagap)	Cefaclor monohydrate	Cephalosporins
12235	Ceporex 1g Tablet (Galen Ltd)	Cefalexin	Cephalosporins
7909	Velosef 500mg capsules (Bristol-Myers Squibb Pharmaceuticals Ltd)	Cefradine	Cephalosporins
1942	Cefadroxil 500mg capsules	Cefadroxil monohydrate	Cephalosporins
60039	Cefalexin 250mg capsules (Waymade Healthcare Plc)	Cefalexin	Cephalosporins
29464	Cefalexin 250mg/5ml oral suspension (Generics (UK) Ltd)	Cefalexin	Cephalosporins
42008	Cefalexin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
19184	Cefalexin 500mg capsules (Generics (UK) Ltd)	Cefalexin	Cephalosporins
2976	Cefaclor 500mg capsules	Cefaclor monohydrate	Cephalosporins
3831	Suprax Paediatric 100mg/5ml oral suspension (Sanofi)	Cefixime	Cephalosporins
61268	Cefuroxime 250mg tablets (Waymade Healthcare Plc)	Cefuroxime axetil	Cephalosporins
44755	Cefalexin 500mg Capsule (Berk Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
28722	Keflex 250mg/5ml oral suspension (Flynn Pharma Ltd)	Cefalexin	Cephalosporins
31825	Cefalexin 250mg tablets (IVAX Pharmaceuticals UK Ltd)	Cefalexin	Cephalosporins
36599	Cefalexin 250mg capsules (Ranbaxy (UK) Ltd)	Cefalexin	Cephalosporins
32643	Cefalexin 500mg capsules (A A H Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
58623	Cefuroxime 250mg tablets (Alliance Healthcare (Distribution) Ltd)	Cefuroxime axetil	Cephalosporins
19133	Cefalexin 250mg capsules (IVAX Pharmaceuticals UK Ltd)	Cefalexin	Cephalosporins
1860	Cefalexin 250mg/5ml oral	Cefalexin	Cephalosporins

	suspension		
21835	Kiflone 250mg Capsule (Berk Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
3846	Zinnat 250mg tablets (GlaxoSmithKline UK Ltd)	Cefuroxime axetil	Cephalosporins
22042	Distaclor 250mg/5ml oral suspension (Flynn Pharma Ltd)	Cefaclor monohydrate	Cephalosporins
41825	Cefalexin 250mg/5ml Oral solution (C P Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
34133	Cefalexin 250mg/5ml oral suspension sugar free (Teva UK Ltd)	Cefalexin	Cephalosporins
565	Cefradine 250mg capsules	Cefradine	Cephalosporins
40945	Ceporex 250mg/5ml syrup (Co-Pharma Ltd)	Cefalexin	Cephalosporins
2428	Distaclor 125mg/5ml Liquid (Dista Products Ltd)	Cefaclor monohydrate	Cephalosporins
30771	Cefaclor 500mg capsules (Ranbaxy (UK) Ltd)	Cefaclor monohydrate	Cephalosporins
26992	Kiflone 500mg Tablet (Berk Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
30789	Cefradine 250mg capsules (Generics (UK) Ltd)	Cefradine	Cephalosporins
3609	Ceporex 125mg/5ml Oral solution (Galen Ltd)	Cefalexin	Cephalosporins
21979	Kiflone 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
59406	Cefalexin 500mg tablets (Waymade Healthcare Plc)	Cefalexin	Cephalosporins
7526	Cefaclor 125mg/5ml oral suspension sugar free	Cefaclor monohydrate	Cephalosporins
13910	Cefaclor 125mg/5ml Liquid (Generics (UK) Ltd)	Cefaclor monohydrate	Cephalosporins
36701	Cefalexin 250mg tablets (Generics (UK) Ltd)	Cefalexin	Cephalosporins
1146	Cefalexin 250mg tablets	Cefalexin	Cephalosporins
59269	Cefalexin 250mg capsules (DE Pharmaceuticals)	Cefalexin	Cephalosporins
19161	Cefalexin 500mg capsules (Ranbaxy (UK) Ltd)	Cefalexin	Cephalosporins
1110	Cefixime 100mg/5ml oral suspension	Cefixime	Cephalosporins
24090	Cefalexin 250mg capsules (PLIVA Pharma Ltd)	Cefalexin	Cephalosporins
33605	Nicef 500mg capsules (Co-Pharma Ltd)	Cefradine	Cephalosporins
17881	Ceftibuten 180mg/5ml suspension	Ceftibuten	Cephalosporins
18451	Cefalexin 1g tablets	Cefalexin	Cephalosporins
4454	Cefradine 500mg capsules	Cefradine	Cephalosporins
1713	Cefalexin 250mg/5ml suspension	Cefalexin	Cephalosporins
22321	Cefalexin 500mg tablets (Generics (UK) Ltd)	Cefalexin	Cephalosporins
12248	Cefalexin 125mg/1.25ml paediatric drops	Cefalexin	Cephalosporins
7430	Keflex 250mg Capsule (Eli	Cefalexin	Cephalosporins

	Lilly and Company Ltd)		
27254	Tenkorex 500mg Capsule (OPD Pharm)	Cefalexin	Cephalosporins
155	Cefalexin 250mg capsules	Cefalexin	Cephalosporins
60202	Cefalexin 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	Cefalexin	Cephalosporins
62188	Cefalexin 250mg capsules (Phoenix Healthcare Distribution Ltd)	Cefalexin	Cephalosporins
61418	Cefadroxil 500mg capsules (Sigma Pharmaceuticals Plc)	Cefadroxil monohydrate	Cephalosporins
58463	Cefuroxime 250mg tablets (Sandoz Ltd)	Cefuroxime axetil	Cephalosporins
13412	Zinnat 125mg/5ml oral suspension (GlaxoSmithKline UK Ltd)	Cefuroxime axetil	Cephalosporins
9689	Cefalexin 500mg tablets (Teva UK Ltd)	Cefalexin	Cephalosporins
7560	Ceporex 125mg/5ml Liquid (Galen Ltd)	Cefalexin	Cephalosporins
32235	Cefaclor 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Cefaclor monohydrate	Cephalosporins
40915	Ceporex 500mg capsules (Co-Pharma Ltd)	Cefalexin	Cephalosporins
Macrolides			
52029	Zithromax 250mg capsules (Mawdsley-Brooks & Company Ltd)	Azithromycin dihydrate	Macrolides
34869	Erythromycin 500mg Tablet (C P Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
54903	Clarithromycin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Clarithromycin	Macrolides
2429	Erythromycin ethyl succinate 125mg/5ml oral suspension	Erythromycin ethyl succinate	Macrolides
55589	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Erythromycin ethyl succinate	Macrolides
58841	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
34795	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Erythromycin ethyl succinate	Macrolides
34779	Erythromycin ethyl succinate 125mg/5ml oral suspension (Sandoz Ltd)	Erythromycin ethyl succinate	Macrolides
46696	Erythromycin ethyl succinate 250mg/5ml oral suspension (Sandoz Ltd)	Erythromycin ethyl succinate	Macrolides
57267	Clarithromycin 125mg/5ml oral suspension (Waymade	Clarithromycin	Macrolides

	Healthcare Plc)		
825	Erythroped pi 125mg/5ml Oral suspension (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
61612	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Erythromycin ethyl succinate	Macrolides
52719	Clarithromycin 250mg tablets (Apotex UK Ltd)	Clarithromycin	Macrolides
60263	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Erythromycin ethyl succinate	Macrolides
3572	Erythroped 250mg Powder (Abbott Laboratories Ltd)	Erythromycin Ethyl Succinate	Macrolides
41604	Erythromycin 500mg Tablet (Hillcross Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
40784	Clarithromycin 500mg tablets (Sandoz Ltd)	Clarithromycin	Macrolides
49952	Erythromycin 250mg gastro-resistant capsules (Phoenix Healthcare Distribution Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
58206	Azithromycin 250mg tablets (Teva UK Ltd)	Azithromycin	Macrolides
58902	Clarithromycin 500mg tablets (Phoenix Healthcare Distribution Ltd)	Clarithromycin	Macrolides
3209	Erythromid 250mg Tablet (Abbott Laboratories Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
50580	Erythromycin 250mg gastro-resistant capsules (Actavis UK Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
48101	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Focus Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
25751	Erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free	Erythromycin Ethyl Succinate	Macrolides
60805	Clarithromycin 500mg tablets (Waymade Healthcare Plc)	Clarithromycin	Macrolides
51426	Clarithromycin 500mg tablets (Accord Healthcare Ltd)	Clarithromycin	Macrolides
52428	Erythromycin 250mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
53875	Clarithromycin 500mg tablets (Tillomed Laboratories Ltd)	Clarithromycin	Macrolides
25595	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Erythromycin ethyl succinate	Macrolides
45870	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Pinewood Healthcare)	Erythromycin ethyl succinate	Macrolides

48163	Clarithromycin 250mg tablets (Actavis UK Ltd)	Clarithromycin	Macrolides
4153	Erythrolar 250mg/5ml Liquid (Lagap)	Erythromycin ethyl succinate	Macrolides
50946	Clarithromycin 250mg tablets (Sigma Pharmaceuticals Plc)	Clarithromycin	Macrolides
58760	Erythroped A 500mg tablets (Necessity Supplies Ltd)	Erythromycin ethyl succinate	Macrolides
57660	Clarithromycin 250mg tablets (Almus Pharmaceuticals Ltd)	Clarithromycin	Macrolides
60382	Azithromycin 250mg capsules (DE Pharmaceuticals)	Azithromycin dihydrate	Macrolides
5357	Clarithromycin 250mg/5ml oral suspension	Clarithromycin	Macrolides
63	Erythromycin 250mg gastro-resistant tablets	Erythromycin	Macrolides/Oral Antibacterials For Acne
9583	Klaricid 250mg/5ml Oral suspension (Abbott Laboratories Ltd)	Clarithromycin	Macrolides
54897	Clarithromycin 250mg tablets (Tillomed Laboratories Ltd)	Clarithromycin	Macrolides
59100	Erythromycin 250mg gastro-resistant tablets (Waymade Healthcare Plc)	Erythromycin	Macrolides/Oral Antibacterials For Acne
681	Clarithromycin 500mg tablets	Clarithromycin	Macrolides
49978	Erythromycin ethyl succinate 125mg/5ml oral suspension (Focus Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
61264	Erythromycin 250mg gastro-resistant tablets (DE Pharmaceuticals)	Erythromycin	Macrolides/Oral Antibacterials For Acne
6121	Klaricid XL 500mg tablets (Abbott Laboratories Ltd)	Clarithromycin	Macrolides
14171	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free	Erythromycin ethyl succinate	Macrolides
54208	Clarithromycin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)	Clarithromycin	Macrolides
54529	Clarithromycin 500mg Modified-release tablet (Hillcross Pharmaceuticals Ltd)	Clarithromycin	Macrolides
103	Erythromycin 250mg gastro-resistant capsules	Erythromycin	Macrolides/Oral Antibacterials For Acne
318	Erymax 250mg Capsule (Elan Pharma)	Erythromycin	Macrolides/Oral Antibacterials For Acne
39613	Erythrocin 500 tablets (AMCo)	Erythromycin stearate	Macrolides
55148	Clarithromycin 250mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Clarithromycin	Macrolides
34189	Erythromycin 250mg Tablet (C P Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
36544	Arpimycin 125mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides

6497	Clarithromycin 500mg with metronidazole 400mg with lansoprazole 30mg triple pack	Metronidazole	Proton Pump Inhibitors/Macrolides
53086	Clarithromycin 250mg tablets (DE Pharmaceuticals)	Clarithromycin	Macrolides
53004	Erythrocin 500 tablets (Necessity Supplies Ltd)	Erythromycin stearate	Macrolides
23017	Erycen 500mg Tablet (Berk Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
32898	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
27504	Primacine 500mg/5ml Liquid (Pinewood Healthcare)	Erythromycin ethyl succinate	Macrolides
30980	Erythromycin ethyl succinate 500mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
23954	Erythrolar 500mg Tablet (Lagap)	Erythromycin stearate	Macrolides
29154	Erythromycin 250mg Capsule (Actavis UK Ltd)	Erythromycin Lactobionate	Macrolides/Oral Antibacterials For Acne
31530	Erythromycin 250mg gastro-resistant tablets (Ranbaxy (UK) Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
39616	Erythrocin 250 tablets (AMCo)	Erythromycin stearate	Macrolides
52952	Erythromycin 250mg gastro-resistant tablets (Co-Pharma Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
33686	Erythromycin 250mg gastro-resistant capsules (A A H Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
27768	Erythrolar 250mg Tablet (Lagap)	Erythromycin stearate	Macrolides
19330	Ilosone 250mg/5ml Liquid (Dista Products Ltd)	Erythromycin Lactobionate	Macrolides/Oral Antibacterials For Acne
32902	Erythromycin ethyl succinate 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
53688	Clarithromycin 250mg tablets (Ranbaxy (UK) Ltd)	Clarithromycin	Macrolides
33248	Erythromycin 125mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd)	Erythromycin ethyl succinate	Macrolides
33304	Kerymax 250mg gastro-resistant capsules (Kent Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
61561	Erythromycin ethyl succinate 250mg/5ml oral suspension (Waymade Healthcare Plc)	Erythromycin ethyl succinate	Macrolides
55133	Erythromycin 250mg gastro-resistant capsules (Kent Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
34974	Clarithromycin 500mg tablets (Teva UK Ltd)	Clarithromycin	Macrolides
49939	Clarithromycin 500mg tablets	Clarithromycin	Macrolides

	(Alliance Healthcare (Distribution) Ltd)		
13120	Erythromycin ethyl succinate 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
54269	Clarithromycin 250mg tablets (Somex Pharma)	Clarithromycin	Macrolides
438	Erythromycin stearate 250mg tablets	Erythromycin stearate	Macrolides
5057	Azithromycin 200mg/5ml oral suspension	Azithromycin	Macrolides
553	Erythromycin 250mg.5ml oral suspension	Erythromycin Ethyl Succinate	Macrolides
54098	Erythroped A 500mg tablets (Lexon (UK) Ltd)	Erythromycin ethyl succinate	Macrolides
60814	Azithromycin 500mg tablets (DE Pharmaceuticals)	Azithromycin	Macrolides
765	Clarithromycin 250mg granules sachets	Clarithromycin	Macrolides
5335	Zithromax 500mg tablets (Pfizer Ltd)	Azithromycin	Macrolides
42661	Erythromycin 250mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
40218	Azithromycin 500mg tablets (Teva UK Ltd)	Azithromycin	Macrolides
55300	Erythromycin 500mg Tablet (Teva UK Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
34334	Erythromycin 250mg gastro-resistant tablets (Generics (UK) Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
58037	Clarithromycin 500mg tablets (Almus Pharmaceuticals Ltd)	Clarithromycin	Macrolides
34650	Clarithromycin 250mg tablets (A A H Pharmaceuticals Ltd)	Clarithromycin	Macrolides
27495	Arpimycin 125mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
56203	Erythroped A 500mg tablets (Sigma Pharmaceuticals Plc)	Erythromycin ethyl succinate	Macrolides
41453	Clarithromycin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Clarithromycin	Macrolides
53850	Azithromycin 200mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Azithromycin	Macrolides
14511	Erymax sprinkle 125mg Capsule (Elan Pharma)	Erythromycin	Macrolides
42659	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
4610	Erythroped forte 500mg/5ml Oral suspension (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
6623	Klaricid 500 tablets (Abbott Laboratories Ltd)	Clarithromycin	Macrolides
34811	Clarithromycin 250mg/5ml	Clarithromycin	Macrolides

	oral suspension (Ranbaxy (UK) Ltd)		
34608	Clarithromycin 500mg tablets (Generics (UK) Ltd)	Clarithromycin	Macrolides
18682	Ilosone 125mg/5ml Liquid (Dista Products Ltd)	Erythromycin Lactobionate	Macrolides/Oral Antibacterials For Acne
53179	Clarithromycin 250mg/5ml oral suspension (Sandoz Ltd)	Clarithromycin	Macrolides
53776	Clarithromycin 500mg tablets (DE Pharmaceuticals)	Clarithromycin	Macrolides
59036	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Pinewood Healthcare)	Erythromycin ethyl succinate	Macrolides
33703	Erythromycin 250mg gastro-resistant tablets (Abbott Laboratories Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
25280	Tiloryth 250mg gastro-resistant capsules (Tillomed Laboratories Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
39118	Primacine 250mg/5ml Liquid (Pinewood Healthcare)	Erythromycin ethyl succinate	Macrolides
10190	Erymax 250mg gastro-resistant capsules (Teva UK Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
51154	Clarithromycin 250mg tablets (Kent Pharmaceuticals Ltd)	Clarithromycin	Macrolides
52860	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Erythromycin ethyl succinate	Macrolides
37022	Arpimycin 500mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
15713	Erythromycin ethylsuccinate 500mg sachets	Erythromycin Ethyl Succinate	Macrolides
55428	Clarithromycin 250mg/5ml oral suspension (Waymade Healthcare Plc)	Clarithromycin	Macrolides
39623	Erythroped PI SF 125mg/5ml oral suspension (AMCo)	Erythromycin ethyl succinate	Macrolides
50693	Erythrocin 500 tablets (Sigma Pharmaceuticals Plc)	Erythromycin stearate	Macrolides
54241	Clarithromycin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Clarithromycin	Macrolides
1072	Erythrocin 500 500mg Tablet (Abbott Laboratories Ltd)	Erythromycin stearate	Macrolides
61810	Azithromycin 500mg tablets (A A H Pharmaceuticals Ltd)	Azithromycin	Macrolides
41389	Erythoden 250mg/5ml Liquid (Stevenden Healthcare)	Erythromycin ethyl succinate	Macrolides
5116	Azithromycin 250mg capsules	Azithromycin dihydrate	Macrolides
47582	Clarithromycin 250mg tablets (Sandoz Ltd)	Clarithromycin	Macrolides
34512	Erythromycin 250mg gastro-resistant capsules (Teva UK Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne

41584	Erythromycin 250mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd)	Erythromycin ethyl succinate	Macrolides
2226	Erythromycin ethyl succinate 500mg/5ml oral suspension	Erythromycin ethyl succinate	Macrolides
53144	Clarithromycin 250mg tablets (Wockhardt UK Ltd)	Clarithromycin	Macrolides
537	Clarithromycin 250mg tablets	Clarithromycin	Macrolides
24127	Erythromycin 250mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
25278	Rommix 500mg Tablet (Ashbourne Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
31428	Retcin 250mg Tablet (DDSA Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
39632	Erythroped A 500mg tablets (AMCo)	Erythromycin ethyl succinate	Macrolides
2719	Klaricid 250mg tablets (Abbott Laboratories Ltd)	Clarithromycin	Macrolides
58175	Clarithromycin 500mg tablets (Wockhardt UK Ltd)	Clarithromycin	Macrolides
55397	Erythromycin 250mg gastro-resistant capsules (Waymade Healthcare Plc)	Erythromycin	Macrolides/Oral Antibacterials For Acne
49301	Erythrolar 500mg tablets (Ennogen Pharma Ltd)	Erythromycin stearate	Macrolides
53703	Clarithromycin 500mg tablets (Kent Pharmaceuticals Ltd)	Clarithromycin	Macrolides
13167	Erythromycin ethyl succinate 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
47242	Erythromycin 250mg/5ml Liquid (C P Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
60308	Erythromycin ethyl succinate 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Erythromycin ethyl succinate	Macrolides
397	Erythromycin 125mg/5ml oral suspension	Erythromycin Ethyl Succinate	Macrolides
993	Erythroped forte 500mg/5ml Liquid (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
46488	Clarithromycin 500mg tablets (Ranbaxy (UK) Ltd)	Clarithromycin	Macrolides
9148	Erythromid ds 500mg Tablet (Abbott Laboratories Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
16747	Erythroped 250mg Sachets (Abbott Laboratories Ltd)	Erythromycin Ethyl Succinate	Macrolides
14514	Zithromax 200mg/5ml oral suspension (Pfizer Ltd)	Azithromycin	Macrolides
2225	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free	Erythromycin ethyl succinate	Macrolides
23244	Ilotycin 250mg Tablet (Eli Lilly and Company Ltd)	Erythromycin	Macrolides/Oral Antibacterials For

			Acne
12330	Erythromycin ethylsuccinate 1g sachets	Erythromycin Ethyl Succinate	Macrolides
34837	Erythromycin 250mg Gastro-resistant tablet (Co-Pharma Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
30520	Primacine 125mg/5ml Liquid (Pinewood Healthcare)	Erythromycin ethyl succinate	Macrolides
34394	Clarithromycin 250mg tablets (Generics (UK) Ltd)	Clarithromycin	Macrolides
401	Erythromycin 500mg ec gastro-resistant tablets	Erythromycin	Macrolides/Oral Antibacterials For Acne
2376	Erythromycin ethyl succinate 250mg/5ml oral suspension	Erythromycin ethyl succinate	Macrolides
2326	Erythromycin 500mg/5ml oral suspension	Erythromycin Ethyl Succinate	Macrolides
52906	Erythromycin 250mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
24220	Arpimycin 250mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
733	Erythromycin ethyl succinate 500mg tablets	Erythromycin ethyl succinate	Macrolides
34533	Clarithromycin 250mg tablets (Teva UK Ltd)	Clarithromycin	Macrolides
13635	Erythromycin ethylsuccinate 250mg sachets	Erythromycin Ethyl Succinate	Macrolides
33685	Erythromycin 250mg gastro-resistant tablets (Teva UK Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
14816	Klaricid Adult 250mg granules sachets (Abbott Laboratories Ltd)	Clarithromycin	Macrolides
51831	Clarithromycin 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	Clarithromycin	Macrolides
33694	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Generics (UK) Ltd)	Erythromycin ethyl succinate	Macrolides
54472	Clarithromycin 250mg tablets (Accord Healthcare Ltd)	Clarithromycin	Macrolides
18643	Ilosone 500mg Tablet (Dista Products Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
4489	Erycen 250mg Tablet (Berk Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
47126	Erythromycin ethyl succinate 125mg/5ml oral suspension (Pinewood Healthcare)	Erythromycin ethyl succinate	Macrolides
50948	Erythromycin ethyl succinate 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	Erythromycin ethyl succinate	Macrolides
2350	Erythromycin stearate 500mg tablets	Erythromycin stearate	Macrolides
50694	Erythromycin 250mg gastro-	Erythromycin	Macrolides/Oral

	resistant capsules (Alliance Healthcare (Distribution) Ltd)		Antibacterials For Acne
105	Erythroped 250mg/5ml Liquid (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
34873	Erythromycin 250mg Tablet (Berk Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
45795	Clarithromycin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Clarithromycin	Macrolides
3736	Klaricid 125mg/5ml Oral suspension (Abbott Laboratories Ltd)	Clarithromycin	Macrolides
40073	Erythromycin estolate 250mg/5ml suspension	Erythromycin Lactobionate	Macrolides/Oral Antibacterials For Acne
53109	Clarithromycin 500mg tablets (Somex Pharma)	Clarithromycin	Macrolides
4372	Erythroped forte 500mg Sachets (Abbott Laboratories Ltd)	Erythromycin Ethyl Succinate	Macrolides
4165	Zithromax 250mg capsules (Pfizer Ltd)	Azithromycin dihydrate	Macrolides
36514	Arpimycin 250mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
31514	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
27203	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Teva UK Ltd)	Erythromycin ethyl succinate	Macrolides
331	Clarithromycin 125mg/5ml oral suspension	Clarithromycin	Macrolides
59441	Erythromycin ethyl succinate 125mg/5ml oral suspension (DE Pharmaceuticals)	Erythromycin ethyl succinate	Macrolides
62143	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (DE Pharmaceuticals)	Erythromycin ethyl succinate	Macrolides
37694	Erythromycin estolate 500mg tablets	Erythromycin Lactobionate	Macrolides/Oral Antibacterials For Acne
34853	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Teva UK Ltd)	Erythromycin ethyl succinate	Macrolides
46154	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
39642	Erythroped Forte SF 500mg/5ml oral suspension (AMCo)	Erythromycin ethyl succinate	Macrolides
327	Erythroped a 500mg Tablet (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
53449	Erythrocin 500 tablets (Lexon (UK) Ltd)	Erythromycin stearate	Macrolides

53153	Clarithromycin 250mg tablets (Phoenix Healthcare Distribution Ltd)	Clarithromycin	Macrolides
24129	Erythromycin 250mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
60828	Erythromycin 250mg gastro-resistant tablets (Bristol Laboratories Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
58756	Erythromycin ethyl succinate 125mg/5ml oral suspension (Waymade Healthcare Plc)	Erythromycin ethyl succinate	Macrolides
17207	Ilosone 250mg Capsule (Dista Products Ltd)	Erythromycin Lactobionate	Macrolides/Oral Antibacterials For Acne
51984	Erythrocin 500 tablets (Mawdsley-Brooks & Company Ltd)	Erythromycin stearate	Macrolides
29344	Erythromycin 250mg gastro-resistant tablets (Actavis UK Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
39010	Klaricid Paediatric 250mg/5ml oral suspension (Abbott Laboratories Ltd)	Clarithromycin	Macrolides
47676	Erythromycin 500mg/5ml Liquid (C P Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
59126	Erythromycin ethyl succinate 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
48017	Erythoden 125mg/5ml Liquid (Stevenden Healthcare)	Erythromycin ethyl succinate	Macrolides
38163	Clarithromycin 500mg tablets (A A H Pharmaceuticals Ltd)	Clarithromycin	Macrolides
21808	Rommix 125mg/5ml Oral suspension sugar free (Ashbourne Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
45591	Clarie XL 500mg tablets (Teva UK Ltd)	Clarithromycin	Macrolides
26365	Erythromycin 500mg Tablet (IVAX Pharmaceuticals UK Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
30234	Erythromycin ethylsuccinate 125mg sachets	Erythromycin Ethyl Succinate	Macrolides
4596	Erythroped a 1g Sachets (Abbott Laboratories Ltd)	Erythromycin Ethyl Succinate	Macrolides
52411	Klaricid 250mg tablets (Necessity Supplies Ltd)	Clarithromycin	Macrolides
4672	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free	Erythromycin ethyl succinate	Macrolides
49530	Azithromycin 200mg/5ml oral suspension (Sandoz Ltd)	Azithromycin	Macrolides
743	Azithromycin 500mg tablets	Azithromycin	Macrolides
39669	Erythroped SF 250mg/5ml oral suspension (AMCo)	Erythromycin ethyl succinate	Macrolides
55483	Erythromycin 250mg gastro-resistant tablets (Milpharm	Erythromycin	Macrolides/Oral Antibacterials For

	Ltd)		Acne
60190	Erythromycin 250mg gastro-resistant tablets (Waymade Healthcare Plc)	Erythromycin	Macrolides/Oral Antibacterials For Acne
9434	Erymin 250mg/5ml Oral suspension (Elan Pharma)	Erythromycin Ethyl Succinate	Macrolides
11611	Rommix 250 EC tablets (Ashbourne Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
38997	Klaricid Paediatric 125mg/5ml oral suspension (Abbott Laboratories Ltd)	Clarithromycin	Macrolides
33695	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Generics (UK) Ltd)	Erythromycin ethyl succinate	Macrolides
532	Erythroped 250mg/5ml Oral suspension (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
58824	Erythromycin 250mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
30177	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Erythromycin ethyl succinate	Macrolides
42296	Erythromycin 250mg gastro-resistant tablets (Dr Reddy's Laboratories (UK) Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
61830	Clarithromycin 125mg/5ml oral suspension (Sigma Pharmaceuticals Plc)	Clarithromycin	Macrolides
33697	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
14429	Erythromycin 125mg sprinkle capsules	Erythromycin	Macrolides
43400	Clamelle 500mg tablets (Actavis UK Ltd)	Azithromycin	Macrolides
61001	Clarithromycin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	Clarithromycin	Macrolides
48023	Clarithromycin 500mg tablets (Actavis UK Ltd)	Clarithromycin	Macrolides
52158	Clarithromycin 250mg tablets (Alliance Healthcare (Distribution) Ltd)	Clarithromycin	Macrolides
50205	Erythrolar 250mg tablets (Ennogen Pharma Ltd)	Erythromycin stearate	Macrolides
58426	Azithromycin 500mg tablets (Sandoz Ltd)	Azithromycin	Macrolides
46695	Azithromycin 500mg Tablet (Hillcross Pharmaceuticals Ltd)	Azithromycin	Macrolides
997	Erythroped pi 125mg/5ml Liquid (Abbott Laboratories Ltd)	Erythromycin ethyl succinate	Macrolides
37796	Erythromycin estolate 125mg/5ml suspension	Erythromycin Lactobionate	Macrolides/Oral Antibacterials For Acne

9903	Erythromycin estolate 250mg capsules	Erythromycin Lactobionate	Macrolides/Oral Antibacterials For Acne
34479	Erythromycin 250mg gastro-resistant tablets (Sovereign Medical Ltd)	Erythromycin	Macrolides/Oral Antibacterials For Acne
3042	Erythroped pi 125mg Sachets (Abbott Laboratories Ltd)	Erythromycin Ethyl Succinate	Macrolides
31379	Ketek 400mg tablets (Sanofi)	Telithromycin	Macrolides
53168	Clarithromycin 125mg/5ml oral suspension (Sandoz Ltd)	Clarithromycin	Macrolides
6803	Clarithromycin 500mg modified-release tablets	Clarithromycin	Macrolides
33888	Azithromycin 250mg tablets	Azithromycin	Macrolides
480	Erythrocin 250mg Tablet (Abbott Laboratories Ltd)	Erythromycin stearate	Macrolides
34231	Erythromycin 125mg/5ml Liquid (Berk Pharmaceuticals Ltd)	Erythromycin ethyl succinate	Macrolides
50223	Erythrocin 500 tablets (Stephar (U.K.) Ltd)	Erythromycin stearate	Macrolides
33705	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Teva UK Ltd)	Erythromycin ethyl succinate	Macrolides
53986	Erythromycin 250mg gastro-resistant tablets (Medreich Plc)	Erythromycin	Macrolides/Oral Antibacterials For Acne
Broad-spectrum penicillin			
17181	Pivampicillin 175mg sachet	Pivampicillin	Broad-spectrum Penicillins
42485	Clavulanic acid 62mg with amoxicillin 250mg/5ml oral suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
46915	Co-amoxiclav 250mg/125mg tablets (Zentiva)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
54796	Amoxicillin 250mg capsules (Boston Healthcare Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
2174	Amoxil 3g oral powder sachets sucrose free (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34679	Amoxicillin 125mg/5ml oral suspension sugar free (Actavis UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
8680	Talpen 125mg/5ml Oral solution (Beecham Research Laboratories)	Talampicillin Hydrochloride	Broad-spectrum Penicillins
40243	Amoxicillin 250mg/5ml oral suspension sugar free (Actavis UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
29337	Amoxicillin 125mg/5ml Oral solution (Neo Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
951	Flucloxacillin with ampicillin 125mg+125mg Liquid	Ampicillin Trihydrate	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
16589	Talampicillin 125mg/5ml syrup	Talampicillin Hydrochloride	Broad-spectrum Penicillins

55394	Amoxicillin 500mg capsules (Wockhardt UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
58771	Amoxicillin 250mg capsules (DE Pharmaceuticals)	Amoxicillin trihydrate	Broad-spectrum Penicillins
2246	Pondocillin 500mg Tablet (LEO Pharma)	Pivampicillin	Broad-spectrum Penicillins
50742	Co-amoxiclav 500mg/125mg tablets (Actavis UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
28882	Amoxicillin 250mg Capsule (Crosspharma Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
641	Co-amoxiclav 500mg/125mg tablets	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
33706	Amoxicillin 500mg capsules (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
17746	Amoxicillin 375mg soluble tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
53627	Amoxicillin 500mg capsules (Accord Healthcare Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
24396	Flemoxin 750mg Soluble tablet (Paines & Byrne Ltd)	Amoxicillin Trihydrate	Broad-spectrum Penicillins
49321	Augmentin 625mg tablets (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
59588	Co-amoxiclav 125mg/31mg/5ml oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
857	Ampicillin 125mg/5ml oral suspension	Ampicillin	Broad-spectrum Penicillins
54808	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
44154	Co-amoxiclav 500mg/125mg tablets (Zentiva)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
52820	Amoxicillin 500mg capsules (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
42227	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
36054	Amoxicillin 125mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
2171	Amoxil 125mg/1.25ml paediatric oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
22438	Amoram 250mg/5ml oral suspension (LPC Medical (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
59481	Amoxicillin 250mg capsules (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
58494	Co-amoxiclav 250mg/62mg/5ml oral	Amoxicillin trihydrate/Potassium	Broad-spectrum Penicillins

	suspension sugar free (Colorama Pharmaceuticals Ltd)	clavulanate	
44854	Amoxicillin 500mg Capsule (Lagap)	Amoxicillin trihydrate	Broad-spectrum Penicillins
59112	Amoxicillin 125mg/5ml oral suspension sugar free (DE Pharmaceuticals)	Amoxicillin trihydrate	Broad-spectrum Penicillins
14386	Galenamox 125mg/5ml oral suspension (Galen Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54591	Co-amoxiclav 500mg/125mg tablets (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
7570	Pivampicillin 500mg tablet	Pivampicillin	Broad-spectrum Penicillins
31156	Ampitrin 250mg Capsule (OPD Pharm)	Ampicillin	Broad-spectrum Penicillins
26356	Amfipen 500mg Capsule (Yamanouchi Pharma Ltd)	Ampicillin	Broad-spectrum Penicillins
60134	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
38684	Amoxicillin 500mg Capsule (C P Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
585	Amoxicillin 250mg/5ml oral suspension sugar free	Amoxicillin trihydrate	Broad-spectrum Penicillins
41090	Amoxicillin 250mg/5ml oral suspension (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
20432	Clavulanic acid 57mg with amoxicillin 400mg/5ml sugar free suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
27725	Amoxicillin 250mg/5ml oral suspension (Teva UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
25370	Ranclav 375mg tablets (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
51536	Amoxicillin 250mg capsules (Milpharm Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
33699	Amoxicillin 250mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
30783	Co-amoxiclav 250mg/125mg tablets (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
34228	Ampicillin 250mg capsules (A A H Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
34885	Amoxicillin 500mg Capsule (DDSA Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
56591	Augmentin-Duo 400/57 oral suspension (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
31801	Amoxicillin 500mg capsules (Sandoz Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
52666	Augmentin 250/62 SF oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
55047	Amoxicillin 125mg/5ml oral	Amoxicillin trihydrate	Broad-spectrum

	suspension (Sandoz Ltd)		Penicillins
34232	Amoxicillin 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
21967	Vidopen 500mg Capsule (Berk Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
11613	Amix 250 capsules (Ashbourne Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
29356	Co-amoxiclav 500mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
13239	Clavulanic acid 125mg with Amoxicillin 500mg tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
30786	Co-amoxiclav 250mg/125mg tablets (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
54271	Amoxicillin 250mg capsules (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
37755	Amoxicillin 250mg/5ml Oral suspension (Sandoz Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54780	Co-amoxiclav 250mg/62mg/5ml oral suspension (Generics (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
57997	Ampicillin 250mg capsules (Waymade Healthcare Plc)	Ampicillin	Broad-spectrum Penicillins
31014	Amoxicillin 125mg/5ml oral suspension sugar free (Generics (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
5341	Augmentin-Duo 400/57 oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
33110	Amrit 250mg/5ml Liquid (BHR Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
51194	Augmentin-Duo 400/57 oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
51678	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
61207	Amoxicillin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
439	Amoxicillin with Clavulanic acid dispersible tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
6687	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
62	Amoxicillin 125mg/5ml oral suspension	Amoxicillin trihydrate	Broad-spectrum Penicillins
204	Penbritin 250mg Capsule (Beecham Research Laboratories)	Ampicillin	Broad-spectrum Penicillins
13285	Amoxicillin 125mg / Clavulanic acid 31mg/5ml oral suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
49683	Augmentin 625mg tablets	Amoxicillin	Broad-spectrum

	(Waymade Healthcare Plc)	trihydrate/Potassium clavulanate	Penicillins
33343	Amoxicillin 250mg capsules (Actavis UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
47640	Amoxicillin 500mg capsules (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
4318	Penbritin 250mg/5ml Oral solution (Beecham Research Laboratories)	Ampicillin	Broad-spectrum Penicillins
29353	Co-amoxiclav 500mg/125mg tablets (Teva UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
31154	Ampitrin 500mg Capsule (OPD Pharm)	Ampicillin	Broad-spectrum Penicillins
2377	Pondocillin 175mg/5ml Oral suspension sugar free (LEO Pharma)	Pivampicillin	Broad-spectrum Penicillins
33165	Amoxicillin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
29858	Amoxicillin 125mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54222	Amoxicillin 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
41744	Ampicillin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
16612	Clavulanic acid 62mg with amoxicillin 250mg/5ml sugar free suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
33701	Co-amoxiclav 500mg/125mg tablets (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
12540	Pivampicillin 250mg with pivmecillinam 200mg tablet	Pivampicillin	Broad-spectrum Penicillins
34638	Amoxicillin 125mg/5ml oral suspension sugar free (Teva UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
900	Ampicillin 125mg/5ml sugar free suspension	Ampicillin Trihydrate	Broad-spectrum Penicillins
10369	Ampicillin 125mg / Flucloxacillin 125mg oral solution	Ampicillin Trihydrate	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
25832	Pivampicillin 125mg with pivmecillinam 100mg tablet	Pivampicillin	Broad-spectrum Penicillins
51637	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
55312	Co-amoxiclav 250mg/125mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
31669	Pondocillin 120mg Sachets (LEO Pharma)	Pivampicillin	Broad-spectrum Penicillins
32872	Amoxicillin 250mg Capsule (Mepira-Pharm)	Amoxicillin trihydrate	Broad-spectrum Penicillins
4582	Amoxicillin 750mg soluble	Amoxicillin Trihydrate	Broad-spectrum

	tablets		Penicillins
524	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
54185	Amoxicillin 250mg capsules (Wockhardt UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
42815	Amoxicillin 250mg/5ml Mixture (Celltech Pharma Europe Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
37485	Penbritin 125mg/5ml syrup (Chemidex Pharma Ltd)	Ampicillin	Broad-spectrum Penicillins
10603	Penbritin 125mg/5ml Oral solution (Beecham Research Laboratories)	Ampicillin	Broad-spectrum Penicillins
31471	Vidopen 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
49656	Augmentin 625mg tablets (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
926	Ampicillin 500mg capsules	Ampicillin	Broad-spectrum Penicillins
33109	Amrit 125mg/5ml Liquid (BHR Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
15148	Amoxil 500mg Dispersible tablet (SmithKline Beecham Plc)	Amoxicillin Trihydrate	Broad-spectrum Penicillins
17282	Almodan 125mg/5ml syrup (Teva UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
55626	Amoxicillin 125mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Amoxicillin trihydrate	Broad-spectrum Penicillins
43548	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
509	Augmentin 625mg tablets (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
16167	Ampicillin 250mg/5ml sugar free suspension	Ampicillin Trihydrate	Broad-spectrum Penicillins
28874	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
53942	Amoxicillin 125mg / Clavulanic acid 62.5mg/5ml oral suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
13216	Amoxicillin 500mg / Clavulanic acid 125mg tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
34734	Co-amoxiclav 250mg/125mg tablets (Teva UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
45317	Amoxicillin 250mg/5ml Oral solution (Neo Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34775	Amoxicillin 250mg/5ml oral suspension sugar free (Teva UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins

17711	Amopen 500mg Capsule (Yorkshire Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
59042	Amoxicillin 250mg capsules (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
32910	Co-amoxiclav 500mg/125mg tablets (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
59592	Amoxicillin 500mg capsules (Pfizer Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
23967	Amoxicillin 250mg capsules (Teva UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
4010	Amoxil 750mg Sachets (GlaxoSmithKline UK Ltd)	Amoxicillin Trihydrate	Broad-spectrum Penicillins
12378	Amoram 125mg/5ml oral suspension (LPC Medical (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54324	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Actavis UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
41646	Ampicillin 250mg Capsule (Berk Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
34297	Co-amoxiclav 250mg/125mg tablets (Generics (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
3669	Amoxymed 250mg Capsule (Medipharma Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54452	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
30705	Co-amoxiclav 500mg/125mg tablets (Generics (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
13848	Amoxicillin 125mg sugar free powder	Amoxicillin Trihydrate	Broad-spectrum Penicillins
569	Augmentin 250/62 SF oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
52122	Amoxicillin 125mg/5ml oral suspension sugar free (Bristol Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
41415	Co-fluampicil 250mg/250mg capsules (Kent Pharmaceuticals Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Broad-spectrum Penicillins
21345	Bacampicillin HCl 400mg tablets	Bacampicillin	Broad-spectrum Penicillins
25484	Amoxicillin 250mg capsules (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
23740	Amoxicillin 500mg capsules (Generics (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34680	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
37304	Co-amoxiclav 250mg/62mg/5ml oral	Amoxicillin trihydrate/Potassium	Broad-spectrum Penicillins

	suspension sugar free (IVAX Pharmaceuticals UK Ltd)	clavulanate	
50279	Augmentin 625mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
49374	Augmentin 375mg tablets (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
7364	Co-amoxiclav 250mg/62mg/5ml oral suspension	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
50446	Co-amoxiclav 250mg/125mg tablets (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
24150	Amoxicillin 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
51164	Augmentin 125/31 SF oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
106	Ampicillin 250mg/5ml oral suspension	Ampicillin	Broad-spectrum Penicillins
40168	Amoxicillin 3g oral powder sachets sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
59879	Amoxicillin 500mg capsules (DE Pharmaceuticals)	Amoxicillin trihydrate	Broad-spectrum Penicillins
42545	Amoxicillin 125mg/5ml oral suspension (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
52771	Amoxicillin 500mg capsules (Bristol Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
55527	Amoxicillin 500mg capsules (Boston Healthcare Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
485	Amoxicillin 125mg/1.25ml oral suspension paediatric	Amoxicillin trihydrate	Broad-spectrum Penicillins
18786	Amix 500 capsules (Ashbourne Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
20516	Miraxid Liquid (Rpr / Fisons)	Pivampicillin	Broad-spectrum Penicillins
26262	Zoxcil 500mg Capsule (Trinity Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
15039	Penbritin 500mg Capsule (Beecham Research Laboratories)	Ampicillin	Broad-spectrum Penicillins
61407	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Colorama Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
2153	Amoxil 125mg/5ml syrup sucrose free (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
48038	Amoxicillin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
51623	Co-amoxiclav 250mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins

4154	Amoxil fiztab 125mg Tablet (Bencard)	Amoxicillin Trihydrate	Broad-spectrum Penicillins
22415	Amoram 500mg capsules (LPC Medical (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
22016	Almodan 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
46918	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
30745	Amoxicillin 250mg capsules (Generics (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
48683	Augmentin 375mg tablets (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
58057	Amoxicillin 250mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
51382	Amoxicillin 250mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
32148	Amfipen forte 250mg/5ml Oral solution (Yamanouchi Pharma Ltd)	Ampicillin	Broad-spectrum Penicillins
14407	Galenamox 250mg/5ml oral suspension (Galen Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
26174	Ampicillin 500mg capsules (A A H Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
49610	Co-amoxiclav 500mg/125mg tablets (Medreich Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
28870	Amoxicillin 125mg/5ml oral suspension (Teva UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
9242	Flucloxacillin with ampicillin 250mg+250mg Capsule	Ampicillin Trihydrate	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
32622	Amoxicillin 125mg/5ml oral suspension (Generics (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
49065	Amoxicillin 250mg/5ml oral suspension sugar free (Bristol Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
33383	Amoxicillin 3g oral powder sachets sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
42732	Amoxicillin 250mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
49063	Augmentin 375mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
11634	Amix 125 oral suspension (Ashbourne Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
33690	Amoxicillin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
23186	Vidopen 125mg/5ml Oral	Ampicillin	Broad-spectrum

	solution (Berk Pharmaceuticals Ltd)		Penicillins
58520	Ampicillin 250mg capsules (Alliance Healthcare (Distribution) Ltd)	Ampicillin	Broad-spectrum Penicillins
34358	Co-fluampicil 250mg/250mg capsules (Generics (UK) Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Broad-spectrum Penicillins
847	Amoxil 500mg capsules (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
21829	Zoxycil 250mg Capsule (Trinity Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
28871	Co-amoxiclav 250mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
20007	Talampicillin 250mg tablets	Talampicillin Hydrochloride	Broad-spectrum Penicillins
57833	Amoxil 500mg capsules (Waymade Healthcare Plc)	Amoxicillin trihydrate	Broad-spectrum Penicillins
870	Amoxicillin 250mg sugar free chewable tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
33696	Amoxicillin 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
55018	Amoxicillin 250mg/5ml oral suspension (Bristol Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
48147	Co-amoxiclav 250mg/125mg tablets (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
21029	Miraxid 450 Tablet (Rpr / Fisons)	Pivampicillin	Broad-spectrum Penicillins
40148	Co-amoxiclav 500mg/125mg tablets (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
1450	Ampicillin 250mg / Flucloxacillin 250mg capsules	Ampicillin Trihydrate	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
399	Augmentin 375mg tablets (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
1391	Amoxicillin 250mg / Clavulanic acid 125mg tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
34855	Amoxicillin 250mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
43229	Amoxicillin 125mg/5ml Oral suspension (Sandoz Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
31286	Amoxymed 125mg/5ml Oral solution (Medipharma Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
58097	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
53609	Co-amoxiclav 500mg/125mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
42809	Amoxicillin 250mg Capsule (C P Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
503	Amoxicillin 125mg/5ml oral	Amoxicillin trihydrate	Broad-spectrum

	suspension sugar free		Penicillins
32760	Ampitritin 125mg/5ml Liquid (OPD Pharm)	Ampicillin	Broad-spectrum Penicillins
24483	Penbritin 250mg capsules (Chemidex Pharma Ltd)	Ampicillin	Broad-spectrum Penicillins
60034	Co-amoxiclav 250mg/125mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
9925	Clavulanic acid 125mg with Amoxicillin 250mg tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
7737	Amoxil fiztab 500mg Tablet (Bencard)	Amoxicillin Trihydrate	Broad-spectrum Penicillins
34384	Amoxicillin 125mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
38091	Penbritin Forte 250mg/5ml syrup (Chemidex Pharma Ltd)	Ampicillin	Broad-spectrum Penicillins
24203	Respillin 250mg Capsule (OPD Pharm)	Amoxicillin trihydrate	Broad-spectrum Penicillins
35570	Amoxicillin 500mg Capsule (Crosspharma Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
32640	Amoxicillin 250mg/5ml oral suspension (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34857	Amoxicillin 125mg/5ml oral suspension (Actavis UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34001	Amoxicillin 500mg capsules (Teva UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
42822	Amoxicillin 125mg/5ml Mixture (Celltech Pharma Europe Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34972	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
19209	Co-amoxiclav 250mg/125mg tablets (Actavis UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
1722	Amoxicillin 500mg dispersible tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
31535	Amoxicillin 250mg/5ml oral suspension sugar free (Generics (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
40320	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
59153	Amoxicillin 250mg capsules (Waymade Healthcare Plc)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34042	Amoxicillin 250mg capsules (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
2281	Amoxicillin 500mg sugar free chewable tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
56884	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
33570	Amoxicillin 250mg/5ml	Amoxicillin trihydrate	Broad-spectrum

	Mixture (Crosspharma Ltd)		Penicillins
23485	Flu-amp 500mg Capsule (Generics (UK) Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Penicillinase-resistant Penicillins/Broad- spectrum Penicillins
7636	Amoxicillin 250mg / Clavulanic acid 62mg/5ml oral suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
427	Amoxicillin 250mg/5ml oral suspension	Amoxicillin trihydrate	Broad-spectrum Penicillins
61906	Amoxicillin 500mg capsules (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
29697	Amopen 125mg/5ml Liquid (Yorkshire Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
56578	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
21963	Almodan 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
52685	Amoxicillin 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
30528	Amoxicillin 250mg capsules (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
14484	Ampicillin / Cloxacillin 500mg capsules	Cloxacillin	Broad-spectrum Penicillins
1812	Amoxil 250mg/5ml syrup sucrose free (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
9473	Co-fluampicil 125mg/125mg/5ml oral suspension	Flucloxacillin magnesium/Ampicillin trihydrate	Broad-spectrum Penicillins
59432	Amoxicillin 250mg capsules (Accord Healthcare Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
57178	Amoxicillin 3g oral powder sachets sugar free (Mawdsley- Brooks & Company Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
53078	Amoxicillin 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
50002	Amoxicillin 125mg/5ml oral suspension (Bristol Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34760	Amoxicillin 250mg/5ml oral suspension (Actavis UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
1638	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
61299	Co-amoxiclav 125mg/31mg/5ml oral suspension (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
54471	Ampicillin 250mg capsules (Kent Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
51436	Amoxil 500mg capsules (Mawdsley-Brooks &	Amoxicillin trihydrate	Broad-spectrum Penicillins

	Company Ltd)		
33692	Amoxicillin 500mg capsules (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
8209	Ampicillin 125mg/5ml paediatric oral suspension	Ampicillin Trihydrate	Broad-spectrum Penicillins
52207	Augmentin 625mg tablets (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
28875	Amoxicillin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
52058	Amoxicillin 500mg capsules (Medreich Plc)	Amoxicillin trihydrate	Broad-spectrum Penicillins
62102	Amoxicillin 250mg/5ml oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate	Broad-spectrum Penicillins
58803	Co-amoxiclav 250mg/125mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
9343	Amoxicillin 750mg sugar free powder	Amoxicillin Trihydrate	Broad-spectrum Penicillins
33693	Co-amoxiclav 250mg/125mg tablets (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
55846	Ampicillin 125mg/5ml Liquid (C P Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
49048	Augmentin 375mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
41835	Amoxicillin 125mg Powder (IVAX Pharmaceuticals UK Ltd)	Amoxicillin Trihydrate	Broad-spectrum Penicillins
12489	Ambaxin 400mg Tablet (Pharmacia Ltd)	Bacampicillin	Broad-spectrum Penicillins
415	Augmentin 125/31 SF oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
18934	Penbritin 125mg/1.25ml Liquid (Beecham Research Laboratories)	Ampicillin Trihydrate	Broad-spectrum Penicillins
49590	Amoxil 500mg capsules (Lexon (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
46175	Ampicillin 125mg/5ml Oral suspension (Hillcross Pharmaceuticals Ltd)	Ampicillin Trihydrate	Broad-spectrum Penicillins
27714	Amrit 250mg Capsule (BHR Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
10755	Ampicillin 60mg / Cloxacillin 30mg/0.6ml sugar free oral suspension	Cloxacillin	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
33112	Amrit 500mg Capsule (BHR Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
10795	Ampiclox 250mg/5ml Oral solution (Beecham Research Laboratories)	Cloxacillin	Broad-spectrum Penicillins
8906	Amoxicillin 125mg / Clavulanic acid 31mg/5ml oral suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
34493	Co-amoxiclav 500mg/125mg	Amoxicillin	Broad-spectrum

	tablets (Ranbaxy (UK) Ltd)	trihydrate/Potassium clavulanate	Penicillins
22015	Respillin 125mg/5ml Oral solution (OPD Pharm)	Amoxicillin trihydrate	Broad-spectrum Penicillins
115	Ampicillin 250mg capsules	Ampicillin	Broad-spectrum Penicillins
34435	Amoxicillin 250mg Capsule (DDSA Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
18930	Flemoxin 375mg Soluble tablet (Paines & Byrne Ltd)	Amoxicillin Trihydrate	Broad-spectrum Penicillins
48	Amoxicillin 500mg capsules	Amoxicillin trihydrate	Broad-spectrum Penicillins
10200	Co-amoxiclav 125mg/31mg/5ml oral suspension	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
545	Co-amoxiclav 250mg/125mg tablets	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
59740	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
17161	Miraxid Tablet (Rpr / Fisons)	Pivampicillin	Broad-spectrum Penicillins
31281	Penbritin 500mg capsules (Chemidex Pharma Ltd)	Ampicillin	Broad-spectrum Penicillins
59908	Co-amoxiclav 500mg/125mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
24093	Clavulanic acid with amoxicillin dispersible tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
21845	Almodan 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54491	Amoxicillin 250mg capsules (Bristol Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
5454	Co-fluampicil 250mg/250mg capsules	Flucloxacillin sodium/Ampicillin trihydrate	Broad-spectrum Penicillins
21799	Almodan 250mg Capsule (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
24200	Respillin 500mg Capsule (OPD Pharm)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54725	Amoxicillin 500mg capsules (Milpharm Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
11954	Talpen 250mg Tablet (Beecham Research Laboratories)	Talampicillin Hydrochloride	Broad-spectrum Penicillins
62074	Amoxicillin 250mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
53924	Amoxicillin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate	Broad-spectrum Penicillins
50595	Augmentin 125/31 SF oral suspension (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
41647	Ampicillin 500mg capsules (Actavis UK Ltd)	Ampicillin	Broad-spectrum Penicillins
21775	Clavulanic acid 31mg with	Amoxicillin Trihydrate	Broad-spectrum

	amoxicillin 125mg/5ml sugar free oral suspension		Penicillins
30743	Amoxicillin 250mg capsules (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
15192	Amoxicillin 400mg / Clavulanic acid 57mg/5ml sugar free oral suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
20531	Amfipen 250mg Capsule (Yamanouchi Pharma Ltd)	Ampicillin	Broad-spectrum Penicillins
21801	Vidopen 250mg Capsule (Berk Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
21844	Amix 250 oral suspension (Ashbourne Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
52857	Amoxicillin 125mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
31661	Amoxicillin 250mg Capsule (Co-Pharma Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34234	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Teva UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
28872	Amoxicillin 125mg/5ml Mixture (Crosspharma Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
14396	Galenamox 500mg capsules (Galen Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
8960	Pondocillin plus Tablet (Edwin Burgess Ltd)	Pivampicillin	Broad-spectrum Penicillins
34714	Amoxicillin 250mg Capsule (Neo Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
8614	Pivampicillin 175mg/5ml oral solution	Pivampicillin	Broad-spectrum Penicillins
19648	Co-fluampicil 250mg/250mg capsules (A A H Pharmaceuticals Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Broad-spectrum Penicillins
42240	Amoxicillin 125mg/5ml Oral solution (Co-Pharma Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
31423	Amopen 250mg/5ml Liquid (Yorkshire Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
60281	Co-amoxiclav 125mg/31mg/5ml oral suspension (CST Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
41818	Amoxicillin 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
3742	Amoxicillin 125mg sugar free chewable tablets	Amoxicillin Trihydrate	Broad-spectrum Penicillins
26157	Amoxicillin 500mg capsules (Actavis UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
41734	Amoxicillin 3g Powder (Actavis UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
60027	Amoxicillin 250mg/5ml oral suspension sugar free (DE Pharmaceuticals)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34852	Amoxicillin 500mg capsules (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
133	Amoxil 250mg capsules	Amoxicillin trihydrate	Broad-spectrum

	(GlaxoSmithKline UK Ltd)		Penicillins
24006	Clavulanic acid 31mg with amoxicillin 125mg/5ml oral suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
55499	Amoxicillin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
45267	Amoxicillin 250mg Capsule (Regent Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
1140	Amoxicillin 3g oral powder sachets sugar free	Amoxicillin trihydrate	Broad-spectrum Penicillins
33222	Amoxicillin 250mg Capsule (Lagap)	Amoxicillin trihydrate	Broad-spectrum Penicillins
19414	Co-amoxiclav 250mg/125mg tablets (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
27681	Ranclav 125mg/31mg/5ml SF oral suspension (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
21827	Almodan 500mg Capsule (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
56561	Amoxicillin 125mg/5ml oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate	Broad-spectrum Penicillins
1637	Amoxil fiztab 250mg Tablet (Bencard)	Amoxicillin Trihydrate	Broad-spectrum Penicillins
57081	Co-amoxiclav 500mg/125mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
22017	Respillin 125mg/5ml Oral solution (OPD Pharm)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54732	Co-amoxiclav 125mg/31mg/5ml oral suspension (Generics (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
56223	Amoxicillin 250mg/5ml oral suspension (Sandoz Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
53996	Co-amoxiclav 500mg/125mg tablets (Aurobindo Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
60267	Amoxicillin 250mg/5ml oral suspension (DE Pharmaceuticals)	Amoxicillin trihydrate	Broad-spectrum Penicillins
59391	Amoxicillin 125mg/5ml oral suspension (DE Pharmaceuticals)	Amoxicillin trihydrate	Broad-spectrum Penicillins
58053	Amoxicillin 250mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54052	Co-amoxiclav 125mg/31mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
56700	Amoxil 500mg capsules (Necessity Supplies Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
57966	Amoxicillin 250mg capsules (Medreich Plc)	Amoxicillin trihydrate	Broad-spectrum Penicillins
54708	Co-amoxiclav 250mg/62mg/5ml oral	Amoxicillin trihydrate/Potassium	Broad-spectrum Penicillins

	suspension (A A H Pharmaceuticals Ltd)	clavulanate	
22452	Britcin 250mg Capsule (DDSA Pharmaceuticals Ltd)	Ampicillin	Broad-spectrum Penicillins
244	Augmentin Intravenous 1.2g powder for solution for injection vials (GlaxoSmithKline UK Ltd)	Amoxicillin sodium/Potassium clavulanate	Broad-spectrum Penicillins
57886	Amoxil 500mg capsules (Stephar (U.K.) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
34912	Amoxicillin 500mg Capsule (Neo Laboratories Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
28130	Amoxicillin 3g oral powder sachets sugar free (Teva UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
14371	Galenamox 250mg capsules (Galen Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
30498	Amopen 250mg Capsule (Yorkshire Pharmaceuticals Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
22029	Amiclav 250mg/125mg tablets (Ashbourne Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
33689	Amoxicillin 250mg/5ml oral suspension (Generics (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
40238	Amoxicillin 250mg/5ml Mixture (Mepra-Pharm)	Amoxicillin trihydrate	Broad-spectrum Penicillins
9243	Amoram 250mg capsules (LPC Medical (UK) Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
32347	Amfipen 125mg/5ml Oral solution (Yamanouchi Pharma Ltd)	Ampicillin	Broad-spectrum Penicillins
48006	Amoxicillin 250mg capsules (Sandoz Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
50341	Co-amoxiclav 500mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	Broad-spectrum Penicillins
23238	Amoxicillin 125mg/5ml oral suspension (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
9	Amoxicillin 250mg capsules	Amoxicillin trihydrate	Broad-spectrum Penicillins
29463	Amoxicillin 500mg capsules (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	Broad-spectrum Penicillins
13262	Amoxicillin 250mg / Clavulanic acid 62mg/5ml oral suspension	Amoxicillin Trihydrate	Broad-spectrum Penicillins
Penicillinase-resistant penicillins (flucloxacillin)			
52281	Flucloxacillin 500mg capsules (Milpharm Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
23240	Flucloxacillin 250mg capsules (A A H Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34226	Flucloxacillin 500mg capsules (Kent Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
308	Magnapen 250mg/250mg capsules (Wockhardt UK Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Penicillinase-resistant Penicillins

951	Flucloxacillin with ampicillin 125mg+125mg Liquid	Ampicillin Trihydrate	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
41172	Flucloxacillin 250mg/5ml oral solution sugar free	Flucloxacillin Sodium	Penicillinase-resistant Penicillins
57292	Flucloxacillin 250mg/5ml oral solution sugar free (Waymade Healthcare Plc)		Penicillinase-resistant Penicillins
34617	Flucloxacillin 500mg capsules (Sandoz Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
58126	Flucloxacillin sodium 125mg/5ml oral suspension	Flucloxacillin sodium	Penicillinase-resistant Penicillins
22422	Galfloxin 250mg Capsule (Galen Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34776	Flucloxacillin 500mg capsules (Generics (UK) Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34330	Flucloxacillin 250mg capsules (Generics (UK) Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
4074	Flucloxin 500mg Capsule (OPD Pharm)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34052	Flucloxacillin 500mg capsules (IVAX Pharmaceuticals UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
57485	Flucloxacillin 500mg capsules (Alliance Healthcare (Distribution) Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
60593	Flucloxacillin 125mg/5ml oral solution (Medreich Plc)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34701	Flucloxacillin 125mg/5ml oral solution (IVAX Pharmaceuticals UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
10461	Cloxacillin 500mg capsules	Cloxacillin	Penicillinase-resistant Penicillins
41163	Flucloxacillin 125mg/5ml oral solution sugar free	Flucloxacillin Sodium	Penicillinase-resistant Penicillins
34007	Flucloxacillin 500mg capsules (Teva UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
25570	Co-fluampicil 250mg/250mg capsules (Sandoz Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Penicillinase-resistant Penicillins
28284	Flucloxacillin 125mg/5ml oral solution (Teva UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
457	Flucloxacillin 125mg/5ml oral solution	Flucloxacillin sodium	Penicillinase-resistant Penicillins
51262	Flucloxacillin 125mg/5ml oral solution (Alliance Healthcare (Distribution) Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
21858	Ladropen 500mg capsules (Teva UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
8468	Floxapen 500mg Capsule (Beecham Research Laboratories)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34848	Flucloxacillin 500mg Capsule (C P Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
39989	Floxapen 250mg capsules (Actavis UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
56869	Flucloxacillin 125mg/5ml oral solution (Crescent Pharma Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
55438	Flucloxacillin 250mg/5ml oral solution sugar free (Kent	Flucloxacillin sodium	Penicillinase-resistant Penicillins

	Pharmaceuticals Ltd)		
10369	Ampicillin 125mg / Flucloxacillin 125mg oral solution	Ampicillin Trihydrate	Penicillinase-resistant Penicillins/Broad- spectrum Penicillins
34364	Flucloxacillin 250mg capsules (Sandoz Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
40025	Floxapen 500mg capsules (Actavis UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34944	Flucloxacillin 250mg Capsule (Co-Pharma Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
3708	Floxapen 250mg Capsule (Beecham Research Laboratories)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
2735	Flucloxin 125mg/5ml Liquid (OPD Pharm)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
12083	Ampiclox neonatal 90mg/0.6ml Oral suspension (Beecham Research Laboratories)	Cloxacillin	Penicillinase-resistant Penicillins/Broad- spectrum Penicillins
52374	Flucloxacillin 500mg capsules (Almus Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
60	Flucloxacillin 250mg capsules	Flucloxacillin sodium	Penicillinase-resistant Penicillins
51830	Flucloxacillin 250mg/5ml oral solution sugar free (Actavis UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
55754	Flucloxacillin 125mg/5ml oral solution (Waymade Healthcare Plc)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
58541	Flucloxacillin 250mg capsules (Bristol Laboratories Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
8633	Orbenin 500mg Capsule (Goldshield Pharmaceuticals Ltd)	Cloxacillin	Penicillinase-resistant Penicillins
7703	Cloxacillin 250mg capsules	Cloxacillin	Penicillinase-resistant Penicillins
50820	Flucloxacillin 500mg capsules (Medreich Plc)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
1001	Flucloxacillin 250mg/5ml oral solution	Flucloxacillin sodium	Penicillinase-resistant Penicillins
55799	Flucloxacillin 500mg capsules (Sigma Pharmaceuticals Plc)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
49349	Flucloxacillin 125mg/5ml oral solution sugar free (Kent Pharmaceuticals Ltd)		Penicillinase-resistant Penicillins
52340	Cloxacillin 30mg with Ampicillin 60mg/0.6ml suspension	Cloxacillin	Penicillinase-resistant Penicillins/Broad- spectrum Penicillins
34464	Flucloxacillin 500mg capsules (Actavis UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
30764	Co-fluampicil 250mg/250mg capsules (IVAX Pharmaceuticals UK Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Penicillinase-resistant Penicillins
9242	Flucloxacillin with ampicillin 250mg+250mg Capsule	Ampicillin Trihydrate	Penicillinase-resistant Penicillins/Broad- spectrum Penicillins
8634	Orbenin 250mg Capsule (Goldshield Pharmaceuticals Ltd)	Cloxacillin	Penicillinase-resistant Penicillins

57415	Flucloxacillin 125mg/5ml oral solution (Phoenix Healthcare Distribution Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
47125	Flucloxacillin 125mg/5ml oral solution sugar free (Actavis UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34313	Flucloxacillin 500mg capsules (A A H Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
4008	Fluclomix 500 capsules (Ashbourne Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
32065	Flucloxacillin 250mg/5ml Oral solution (Teva UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
31775	Flucloxacillin 250mg/5ml oral solution (A A H Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
51037	Flucloxacillin 250mg capsules (Alliance Healthcare (Distribution) Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
579	Flucloxacillin 500mg capsules	Flucloxacillin sodium	Penicillinase-resistant Penicillins
1450	Ampicillin 250mg / Flucloxacillin 250mg capsules	Ampicillin Trihydrate	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
34375	Flucloxacillin 250mg capsules (Kent Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34380	Co-fluampicil 250mg/250mg capsules (Actavis UK Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Penicillinase-resistant Penicillins
33993	Flucloxacillin 250mg capsules (Teva UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
21806	Ladropen 250mg capsules (Teva UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34721	Flucloxacillin 250mg capsules (IVAX Pharmaceuticals UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
40108	Flucloxacillin 250mg capsules (Almus Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
56027	Flucloxacillin 250mg capsules (Sigma Pharmaceuticals Plc)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
23485	Flu-amp 500mg Capsule (Generics (UK) Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
57106	Flucloxacillin 250mg capsules (Medreich Plc)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
29944	Flucloxacillin 250mg capsules (Ranbaxy (UK) Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
57462	Flucloxacillin 250mg/5ml oral solution (Crescent Pharma Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
43546	Flucloxacillin 125mg/5ml oral solution (Actavis UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
54907	Cloxacillin 250mg with Ampicillin 250mg injection	Cloxacillin	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
21850	Zoxin 250mg Capsule (Opus Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
8282	Cloxacillin 125mg/5ml oral solution	Cloxacillin	Penicillinase-resistant Penicillins
2874	Magnapen syrup (Wockhardt UK Ltd)	Flucloxacillin magnesium/Ampicillin	Penicillinase-resistant Penicillins

		trihydrate	
45312	Flucloxacillin 125mg/5ml Liquid (Lagap)	Flucloxacillin magnesium	Penicillinase-resistant Penicillins
10755	Ampicillin 60mg / Cloxacillin 30mg/0.6ml sugar free oral suspension	Cloxacillin	Penicillinase-resistant Penicillins/Broad-spectrum Penicillins
34766	Flucloxacillin 125mg/5ml oral solution (Kent Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
57634	Flucloxacillin 250mg capsules (Milpharm Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
60032	Flucloxacillin 125mg/5ml oral solution (Milpharm Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
27057	Flucloxacillin 125mg/5ml oral solution (A A H Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
56384	Flucloxacillin 500mg capsules (Bristol Laboratories Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
25834	Orbenin 125mg/5ml Oral solution (Goldshield Pharmaceuticals Ltd)	Cloxacillin	Penicillinase-resistant Penicillins
32665	Galfloxin 500mg Capsule (Galen Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
24747	Ladropen 125mg/5ml Liquid (Berk Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34259	Flucloxacillin 125mg/5ml oral solution (Sandoz Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
50729	Flucloxacillin 250mg/5ml oral solution (DE Pharmaceuticals)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34683	Flucloxacillin 125mg/5ml oral solution (Generics (UK) Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
32361	Stafoxil 250mg Capsule (Yamanouchi Pharma Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
44855	Flucloxacillin 500mg capsules (Ranbaxy (UK) Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34870	Flucloxacillin 250mg Capsule (C P Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
45252	Flucloxacillin 500mg Capsule (Co-Pharma Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
9800	Flucloxin 250mg Capsule (OPD Pharm)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
2299	Fluclomix 250 capsules (Ashbourne Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
34057	Flucloxacillin 250mg capsules (Actavis UK Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
52549	Flucloxacillin 250mg/5ml oral solution (Phoenix Healthcare Distribution Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
61896	Flucloxacillin 125mg/5ml oral solution sugar free (Waymade Healthcare Plc)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
32901	Flucloxacillin 250mg/5ml oral solution (Kent Pharmaceuticals Ltd)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
60260	Flucloxacillin 500mg capsules (DE Pharmaceuticals)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
56189	Flucloxacillin 250mg/5ml oral solution sugar free (A A H	Flucloxacillin sodium	Penicillinase-resistant Penicillins

	Pharmaceuticals Ltd)		
31940	Flucloxacillin 250mg/5ml Oral solution (Lagap)	Flucloxacillin sodium	Penicillinase-resistant Penicillins
Pen V penicillin			
25293	Apsin vk 250mg Tablet (Approved Prescription Services Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
46902	Penicillin VK 125mg/5ml Oral solution (Sandoz Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
54727	Phenoxymethylpenicillin 250mg/5ml oral solution (Ennogen Healthcare Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
50001	Phenoxymethylpenicillin 250mg/5ml oral solution (Crescent Pharma Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34363	Penicillin V 125mg/5ml Oral solution (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
42211	Phenoxymethylpenicillin 250mg tablets (Almus Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
30233	Phenoxymethylpenicillin 250mg/5ml oral solution (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
44692	Penicillin VK 250mg Tablet (C P Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
45022	Penicillin V 125mg/5ml Oral solution (Sovereign Medical Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
56251	Phenoxymethylpenicillin 125mg/5ml oral solution sugar free (Cubic Pharmaceuticals Ltd)		Benzylpenicillin And Phenoxymethylpenicillin
34156	Penicillin VK 250mg/5ml Oral solution (Lagap)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34675	Phenoxymethylpenicillin 125mg/5ml oral solution (IVAX Pharmaceuticals UK Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
10079	Penicillin V 250mg/5ml oral solution sugar free	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
38241	Phenoxymethylpenicillin 250mg tablets (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
49166	Phenoxymethylpenicillin 250mg tablets (Alliance Healthcare (Distribution) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
49064	Phenoxymethylpenicillin 250mg tablets (Medreich Plc)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34183	Phenoxymethylpenicillin 62.5mg/5ml oral solution	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
481	Penicillin V 250mg/5ml syrup	Phenoxymethylpenicillin	Benzylpenicillin And

		Potassium	Phenoxymethylpenicillin
44354	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (Sandoz Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
54310	Phenoxymethylpenicillin 125mg/5ml oral solution (Bristol Laboratories Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
54552	Phenoxymethylpenicillin 250mg/5ml oral solution (Bristol Laboratories Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
48207	Phenoxymethylpenicillin 333mg tablet	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
47241	Phenoxymethylpenicillin 125mg/5ml oral solution (Almus Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
49236	Phenoxymethylpenicillin 250mg tablets (Kent Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
55311	Phenoxymethylpenicillin 250mg tablets (Waymade Healthcare Plc)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
10647	V-cil-k 250mg Tablet (Eli Lilly and Company Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34255	Phenoxymethylpenicillin 250mg tablets (A A H Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34254	Phenoxymethylpenicillin 125mg/5ml oral solution (A A H Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
48140	Phenoxymethylpenicillin 250mg/5ml oral suspension	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
26659	Distaquaine v-k 250mg/5ml Liquid (Dista Products Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
21405	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
49167	Phenoxymethylpenicillin 250mg tablets (Phoenix Healthcare Distribution Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
45282	Phenoxymethylpenicillin 250mg/5ml oral solution (Sandoz Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
50609	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (Phoenix Healthcare Distribution Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
1783	Penicillin V 125mg tablet	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
31392	Phenoxymethylpenicillin 250mg/5ml oral solution (Actavis UK Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34267	Phenoxymethylpenicillin 125mg/5ml oral solution (Teva	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin

	UK Ltd)		in
53329	Phenoxymethylpenicillin 125mg/5ml oral solution (Crescent Pharma Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
34646	Phenoxymethylpenicillin 250mg/5ml oral solution (IVAX Pharmaceuticals UK Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
15014	Distaquaine v-k 125mg/5ml Liquid (Dista Products Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
53467	Phenoxymethylpenicillin 250mg/5ml oral solution (Sigma Pharmaceuticals Plc)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
53876	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (Alliance Healthcare (Distribution) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
34659	Phenoxymethylpenicillin 250mg/5ml oral solution (Kent Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
45724	Penicillin V 250mg Tablet (Genesis Medical Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
54821	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (Cubic Pharmaceuticals Ltd)		Benzylpenicillin And Phenoxymethylpenicill in
51437	Phenoxymethylpenicillin 125mg/5ml oral solution sugar free (Alliance Healthcare (Distribution) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
45898	Phenoxymethylpenicillin 125mg/5ml oral solution sugar free (Kent Pharmaceuticals Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicill in
34211	Phenoxymethylpenicillin 125mg/5ml oral solution (Actavis UK Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
58367	Penicillin VK 250mg Tablet (Celltech Pharma Europe Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
42222	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
4925	Phenoxymethylpenicillin 250mg/5ml oral solution	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
53652	Phenoxymethylpenicillin 250mg/5ml oral solution (Alliance Healthcare (Distribution) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
56246	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (Waymade Healthcare Plc)		Benzylpenicillin And Phenoxymethylpenicill in
38110	Crystapen v 125mg/5ml Oral solution (Glaxo Laboratories Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
48598	Phenoxymethylpenicillin	Phenoxymethylpenicillin	Benzylpenicillin And

	125mg/5ml oral solution (Medreich Plc)	potassium	Phenoxymethylpenicillin
40248	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (Kent Pharmaceuticals Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
42512	Phenoxymethylpenicillin 250mg/5ml Oral solution (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
57754	Penicillin VK 250mg Tablet (Nucross)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34089	Phenoxymethylpenicillin 250mg capsule	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
34098	Phenoxymethylpenicillin 250mg tablets (Actavis UK Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34424	Phenoxymethylpenicillin 250mg/5ml oral solution (Teva UK Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
26225	Stabilin V-K 250mg/5ml Oral solution (Knoll Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
408	Penicillin V 250mg/5ml oral solution	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
127	Penicillin V 125mg/5ml oral solution	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
34895	Penicillin V 250mg/5ml Oral solution (Celltech Pharma Europe Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34346	Phenoxymethylpenicillin 250mg tablets (Teva UK Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34244	Penicillin VK 125mg/5ml Oral solution (Lagap)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
30231	Phenoxymethylpenicillin 125mg/5ml Oral solution (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
46145	Penicillin V 125mg/5ml Oral solution (C P Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34645	Penicillin V 250mg/5ml Oral solution (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
36524	Apsin vk 125mg/5ml Oral solution (Approved Prescription Services Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
10584	V-cil-k 125mg/5ml Oral solution (Eli Lilly and Company Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
41985	V-cil-k 62.5mg/5ml Oral solution (Eli Lilly and Company Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
52738	Phenoxymethylpenicillin 250mg/5ml oral solution sugar		Benzylpenicillin And Phenoxymethylpenicillin

	free (Bristol Laboratories Ltd)		in
34112	Phenoxymethylpenicillin 250mg/5ml oral solution (A A H Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
43022	Phenoxymethylpenicillin 125mg/5ml oral solution sugar free (A A H Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
100	Penicillin V 250mg capsule	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicill in
10355	V-cil-k 250mg/5ml Oral solution (Eli Lilly and Company Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
32185	Distaquaine v-k 125mg Tablet (Dista Products Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicill in
49807	Phenoxymethylpenicillin 250mg tablets (Bristol Laboratories Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
56942	Phenoxymethylpenicillin 250mg tablets (The Boots Company Plc)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
25694	Penicillin VK 250mg Tablet (Kent Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
26215	Stabilin V-K 250mg Tablet (Knoll Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
45527	Penicillin V 125mg/5ml Oral solution (Celltech Pharma Europe Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
33237	Stabilin V-K 62.5mg/5ml Oral solution (Knoll Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicill in
61102	Phenoxymethylpenicillin 125mg/5ml oral solution (DE Pharmaceuticals)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
51432	Phenoxymethylpenicillin 125mg/5ml oral solution (Sigma Pharmaceuticals Plc)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
54270	Phenoxymethylpenicillin 125mg/5ml oral solution (Ennogen Healthcare Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
18309	Distaquaine v-k 250mg Tablet (Dista Products Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
34105	Phenoxymethylpenicillin 125mg tablet	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicill in
12365	V-cil-k 125mg Tablet (Eli Lilly and Company Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicill in
31534	Penicillin V 250mg Tablet (Sovereign Medical Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in
34756	Penicillin VK 125mg/5ml Oral solution (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicill in

34496	Penicillin V 250mg Tablet (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
43693	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (Teva UK Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
56142	Phenoxymethylpenicillin 125mg/5ml oral solution sugar free (Waymade Healthcare Plc)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
102	Penicillin V 250mg tablet	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
43	Phenoxymethylpenicillin 250mg tablets	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
46424	Phenoxymethylpenicillin 250mg/5ml oral solution (Almus Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
10095	Penicillin V 125mg/5ml oral solution sugar free	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
34956	Phenoxymethylpenicillin 125mg/5ml oral solution (Kent Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
38071	Phenoxymethylpenicillin 250mg/5ml oral solution sugar free (A A H Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
43759	Penicillin VK 250mg Tablet (Lagap)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
43555	Penicillin V 250mg/5ml Oral solution (C P Pharmaceuticals Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
224	Penicillin V 62.5mg/5ml syrup	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
22010	Apsin vk 250mg/5ml Oral solution (Approved Prescription Services Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
13400	V-cil-k 250mg Capsule (Eli Lilly and Company Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
34909	Penicillin VK 250mg Tablet (Sovereign Medical Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
34388	Penicillin VK 250mg Tablet (Generics (UK) Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
43758	Phenoxymethylpenicillin 250mg tablets (Sandoz Ltd)	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
4835	Phenoxymethylpenicillin 125mg/5ml oral solution	Phenoxymethylpenicillin potassium	Benzylpenicillin And Phenoxymethylpenicillin
40906	Phenoxymethylpenicillin 125mg/5ml oral solution sugar free (Teva UK Ltd)	Phenoxymethylpenicillin Potassium	Benzylpenicillin And Phenoxymethylpenicillin
18191	Phenoxymethylpenicillin	Phenoxymethylpenicillin	Benzylpenicillin And

	125mg/5ml oral solution sugar free	Potassium	Phenoxyethylpenicillin
34113	Penicillin VK 250mg Tablet (Berk Pharmaceuticals Ltd)	Phenoxyethylpenicillin potassium	Benzylpenicillin And Phenoxyethylpenicillin
53888	Phenoxyethylpenicillin 666mg tablet	Phenoxyethylpenicillin Potassium	Benzylpenicillin And Phenoxyethylpenicillin
49467	Phenoxyethylpenicillin 125mg/5ml oral solution (Alliance Healthcare (Distribution) Ltd)	Phenoxyethylpenicillin potassium	Benzylpenicillin And Phenoxyethylpenicillin
49832	Phenoxyethylpenicillin 125mg/5ml oral solution sugar free (Phoenix Healthcare Distribution Ltd)	Phenoxyethylpenicillin potassium	Benzylpenicillin And Phenoxyethylpenicillin
Pivmecillinam			
26101	Pivmecillinam 100mg/sachet	Pivmecillinam Hydrochloride	Mecillinams/Urinary-tract Infections
12014	Pivmecillinam 200mg tablets	Pivmecillinam hydrochloride	Mecillinams
12015	Selexid 100mg/sachet Liquid (Edwin Burgess Ltd)	Pivmecillinam Hydrochloride	Mecillinams/Urinary-tract Infections
9601	Selexid 200mg tablets (LEO Pharma)	Pivmecillinam hydrochloride	Mecillinams
Quinolones			
12277	Cinoxacin 500mg capsules	Cinoxacin	Quinolones
54393	Ciprofloxacin 250mg tablets (Arrow Generics Ltd)	Ciprofloxacin hydrochloride	Quinolones
49839	Ciproxin 500mg tablets (Waymade Healthcare Plc)	Ciprofloxacin hydrochloride	Quinolones
51537	Ciprofloxacin 250mg tablets (Alliance Healthcare (Distribution) Ltd)	Ciprofloxacin hydrochloride	Quinolones
34494	Ciprofloxacin 500mg tablets (Wockhardt UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
50601	Ciprofloxacin 250mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	Quinolones
43517	Ciprofloxacin 750mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
56856	Ciprofloxacin 750mg tablets (Ranbaxy (UK) Ltd)	Ciprofloxacin hydrochloride	Quinolones
61302	Ciprofloxacin 100mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	Quinolones
7752	Ciproxin 750mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	Quinolones
53878	Ciprofloxacin 500mg tablets (Ranbaxy (UK) Ltd)	Ciprofloxacin hydrochloride	Quinolones
728	Ciproxin 500mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	Quinolones
58235	Ciprofloxacin 250mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	Quinolones
56789	Ciprofloxacin 500mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	Ciprofloxacin hydrochloride	Quinolones
34322	Ciprofloxacin 500mg Tablet (Niche Generics Ltd)	Ciprofloxacin hydrochloride	Quinolones
1837	Ciprofloxacin 750mg tablets	Ciprofloxacin hydrochloride	Quinolones

34973	Ciprofloxacin 750mg Tablet (Niche Generics Ltd)	Ciprofloxacin hydrochloride	Quinolones
29343	Ciprofloxacin 250mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	Quinolones
45341	Ciprofloxacin 500mg Tablet (Neo Laboratories Ltd)	Ciprofloxacin hydrochloride	Quinolones
50055	Ciprofloxacin 500mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	Quinolones
34605	Ciprofloxacin 500mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
45285	Ciprofloxacin 500mg tablets (Teva UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
42174	Ciprofloxacin 500mg tablets (IVAX Pharmaceuticals UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
52309	Ciprofloxacin 100mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	Quinolones
57960	Ciprofloxacin 500mg tablets (Tillomed Laboratories Ltd)	Ciprofloxacin hydrochloride	Quinolones
52099	Ciprofloxacin 750mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	Quinolones
34308	Ciprofloxacin 250mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
52353	Ciproxin 250mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	Quinolones
34448	Ciprofloxacin 250mg tablets (Niche Generics Ltd)	Ciprofloxacin hydrochloride	Quinolones
53519	Ciproxin 250mg tablets (Lexon (UK) Ltd)	Ciprofloxacin hydrochloride	Quinolones
498	Ciprofloxacin 100mg tablets	Ciprofloxacin hydrochloride	Quinolones
60436	Ciprofloxacin 250mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	Quinolones
61783	Ciprofloxacin 250mg tablets (Waymade Healthcare Plc)	Ciprofloxacin hydrochloride	Quinolones
56381	Ciprofloxacin 250mg tablets (Co-Pharma Ltd)	Ciprofloxacin hydrochloride	Quinolones
52177	Ciproxin 500mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	Quinolones
1202	Ciproxin 250mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	Quinolones
34647	Ciprofloxacin 250mg Tablet (Neo Laboratories Ltd)	Ciprofloxacin hydrochloride	Quinolones
33989	Ciprofloxacin 250mg tablets (Generics (UK) Ltd)	Ciprofloxacin hydrochloride	Quinolones
53641	Ciprofloxacin 500mg tablets (Co-Pharma Ltd)	Ciprofloxacin hydrochloride	Quinolones
55917	Ciprofloxacin 500mg tablets (Medreich Plc)	Ciprofloxacin hydrochloride	Quinolones
59572	Ciprofloxacin 500mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	Quinolones
30707	Ciprofloxacin 500mg tablets (Generics (UK) Ltd)	Ciprofloxacin hydrochloride	Quinolones
58021	Ciprofloxacin 100mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	Quinolones
54302	Ciprofloxacin 250mg tablets (Medreich Plc)	Ciprofloxacin hydrochloride	Quinolones
54555	Ciprofloxacin 100mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	Quinolones

39913	Ciprofloxacin 100mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	Quinolones
4091	Ciprofloxacin 250mg/5ml oral suspension	Ciprofloxacin	Quinolones
34655	Ciprofloxacin 250mg tablets (Wockhardt UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
43557	Ciprofloxacin 500mg tablets (PLIVA Pharma Ltd)	Ciprofloxacin hydrochloride	Quinolones
29472	Ciprofloxacin 750mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	Quinolones
34694	Ciprofloxacin 250mg tablets (PLIVA Pharma Ltd)	Ciprofloxacin hydrochloride	Quinolones
281	Ciprofloxacin 250mg tablets	Ciprofloxacin hydrochloride	Quinolones
34478	Ciprofloxacin 250mg tablets (Teva UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
49445	Ciprofloxacin 500mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	Quinolones
43814	Ciprofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	Quinolones
61869	Ciproxin 250mg/5ml oral suspension (Waymade Healthcare Plc)	Ciprofloxacin	Quinolones
58608	Ciprofloxacin 100mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	Quinolones
42507	Ciprofloxacin 100mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	Quinolones
59937	Ciprofloxacin 750mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	Quinolones
43797	Ciprofloxacin 500mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	Quinolones
9154	Ciproxin 100mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	Quinolones
54674	Ciprofloxacin 100mg tablets (Phoenix Healthcare Distribution Ltd)	Ciprofloxacin hydrochloride	Quinolones
583	Ciprofloxacin 500mg tablets	Ciprofloxacin hydrochloride	Quinolones
53088	Ciprofloxacin 500mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	Quinolones
54701	Ciprofloxacin 250mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	Quinolones
52501	Ciprofloxacin 500mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	Quinolones
41561	Ciprofloxacin 250mg tablets (IVAX Pharmaceuticals UK Ltd)	Ciprofloxacin hydrochloride	Quinolones
52807	Ciproxin 500mg tablets (Mawdsley-Brooks & Company Ltd)	Ciprofloxacin hydrochloride	Quinolones
34559	Ciprofloxacin 250mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	Quinolones
58323	Ciprofloxacin 100mg tablets (Alliance Healthcare (Distribution) Ltd)	Ciprofloxacin hydrochloride	Quinolones
52616	Ciprofloxacin 500mg tablets (Arrow Generics Ltd)	Ciprofloxacin hydrochloride	Quinolones
29458	Ciprofloxacin 500mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	Quinolones

57118	Ciprofloxacin 250mg tablets (Kent Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	Quinolones
Trimethoprim-cotrimoxazole			
51510	Trimethoprim 200mg tablets (Bristol Laboratories Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
34542	Trimethoprim 100mg tablets (Teva UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
41967	Co-trimoxazole 240mg/5ml Oral suspension (Hillcross Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
9100	Co-trimoxazole (trimethoprim and sulfamethoxazole) 160mg+800mg dispersible tablets	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
57981	Trimethoprim 200mg tablets (Waymade Healthcare Plc)	Trimethoprim	Sulphonamides And Trimethoprim
13325	Monotrim 100mg tablets (Abbott Healthcare Products Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
31477	Laratrium Liquid (Lagap)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
42517	Co-trimoxazole 40mg+200mg Liquid (Celltech Pharma Europe Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
7421	Bactrim adult 480mg/5ml Liquid (Roche Products Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
29907	Comox Tablet (IVAX Pharmaceuticals UK Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
8073	Trimethoprim 300mg Tablet	Trimethoprim	Sulphonamides And Trimethoprim/Urinary- tract Infections
34727	Co-trimoxazole 80mg/400mg tablets (Actavis UK Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
53828	Trimethoprim 50mg/5ml oral suspension sugar free (Actavis UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
34488	Trimethoprim 100mg tablets (Kent Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
37	Trimethoprim 200mg tablets	Trimethoprim	Sulphonamides And Trimethoprim
34878	Trimethoprim 100mg Tablet (C P Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary- tract Infections
606	Co-trimoxazole 80mg/400mg tablets	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
53284	Trimethoprim 50mg/5ml oral suspension sugar free (Sigma Pharmaceuticals Plc)	Trimethoprim	Sulphonamides And Trimethoprim
52198	Co-trimoxazole 80mg/400mg tablets (Sigma Pharmaceuticals)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim

	Plc)		
44075	Septin tablets (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
1604	Septin paediatric Oral suspension sugar free (Wellcome Medical Division)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
32908	Trimethoprim 200mg tablets (Teva UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
34252	Trimethoprim 50mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
33997	Trimethoprim 200mg tablets (IVAX Pharmaceuticals UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
25497	Syraprim 100mg Tablet (Wellcome Medical Division)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
303	Co-trimoxazole 16mg with 80mg/ml concentrate solution for infusion	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
41544	Trimethoprim 100mg Tablet (IVAX Pharmaceuticals UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
10745	Bactrim double strength 160mg+800mg Tablet (Roche Products Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
56267	Trimethoprim 100mg tablets (Bristol Laboratories Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
27921	Laratrium forte Tablet (Lagap)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
33987	Sulfamethoxazole 800mg with trimethoprim 160mg/5ml concentrate solution for infusion	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
7616	Trimopan 50mg/5ml Liquid (Berk Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
43505	Trimethoprim 200mg Tablet (Numark Management Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
3660	Septin Dispersible tablet (Wellcome Medical Division)	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
29351	Trimethoprim 50mg/5ml oral suspension sugar free (Teva UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
45246	Trimethoprim 100mg tablets (Sandoz Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
2460	Septin Forte 160mg/800mg tablets (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
32906	Trimethoprim 100mg tablets (A A H Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim

14367	Ipral 50mg/5ml Liquid (E R Squibb and Sons Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
29532	Trimogal 100mg Tablet (Lagap)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
21805	Triprimix 200 Tablet (Ashbourne Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
28004	Co-trimoxazole (trimethoprim and sulfamethoxazole) 20mg+100mg paediatric tablets	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
131	Septin for Infusion 80mg/400mg/5ml solution for infusion ampoules (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
340	Trimethoprim 100mg tablets	Trimethoprim	Sulphonamides And Trimethoprim
33794	Sulfamethoxazole 400mg with trimethoprim 80mg/5ml oral suspension	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
46663	Bactrim paediatric tablets (Roche Products Ltd)	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
403	Sulfadiazine 500mg tablets	Sulfadiazine	Sulphonamides And Trimethoprim/Drugs For Toxoplasmosis
15988	Trimethoprim with sulfamethoxazole 80mg+400mg Tablet	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
2658	Co-trimoxazole 80mg/400mg/5ml oral suspension	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
41991	Co-trimoxazole 80mg+400mg Dispersible tablet (Approved Prescription Services Ltd)	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
44241	Fectrim Dispersible tablet (DDSA Pharmaceuticals Ltd)	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
34379	Trimethoprim 200mg tablets (Kent Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
34392	Trimethoprim 200mg tablets (Actavis UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
7420	Bactrim 480mg Tablet (Roche Products Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
43545	Trimethoprim 100mg tablets (Actavis UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
24324	Trimogal 200mg Tablet (Lagap)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
20126	Trimethoprim with	Sulfamethoxazole	Sulphonamides And

	sulfamethoxazole 160mg+800mg Tablet		Trimethoprim/Drugs For Pneumocystis Pneumonia
10046	Trimopan 200mg tablets (Teva UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
58490	Trimethoprim 100mg tablets (Alliance Healthcare (Distribution) Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
21809	Comixco 80mg+400mg Tablet (Ashbourne Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
10308	Sulfamethoxazole 400mg with trimethoprim 80mg tablet	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
34455	Trimethoprim 200mg Tablet (C P Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary- tract Infections
39933	Trimethoprim 200mg tablets (Almus Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
52669	Trimethoprim 200mg/5ml oral solution		Sulphonamides And Trimethoprim
50120	Trimethoprim 200mg tablets (Accord Healthcare Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
53275	Trimethoprim 50mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
27048	Syraprim 300mg Tablet (Wellcome Medical Division)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary- tract Infections
31484	Laratrim adult 480mg/5ml Liquid (Lagap)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
8561	Bactrim paediatric sugar free oral solution	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
61714	Trimethoprim 50mg/5ml oral suspension sugar free (Pinewood Healthcare)	Trimethoprim	Sulphonamides And Trimethoprim
41978	Co-trimoxazole 240mg/5ml Oral suspension (Approved Prescription Services Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
14998	Ipral 200mg Tablet (E R Squibb and Sons Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary- tract Infections
53276	Trimethoprim 50mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
30614	Sulfamethoxazole 200mg with trimethoprim 40mg/5ml oral suspension	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
31905	Trimethoprim with sulfamethoxazole 80mg + 400mg/5ml Concentrate for	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis

	solution for infusion		Pneumonia
30201	Co-trimoxazole 240mg/5ml Paediatric mixture (Lagap)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
8171	Monotrim 200mg tablets (Abbott Healthcare Products Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
51725	Trimethoprim 20mg/5ml oral suspension		Sulphonamides And Trimethoprim
44286	Septin Paediatric 40mg/200mg/5ml oral suspension (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
135	Septin Tablet (Wellcome Medical Division)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
38090	Co-trimoxazole 480mg/5ml Adult Mixture (Lagap)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
43262	Co-trimoxazole 240mg/5ml Oral suspension (C P Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
50797	Trimethoprim 200mg tablets (Alliance Healthcare (Distribution) Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
27418	Trimethoprim with sulfamethoxazole 40mg + 200mg/5ml Oral suspension	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
43537	Trimethoprim 200mg Tablet (Celltech Pharma Europe Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary- tract Infections
8741	Bactrim Dispersible tablet (Roche Products Ltd)	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
58282	Co-trimoxazole 80mg/400mg tablets (Waymade Healthcare Plc)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
22991	Chemotrim Liquid (Rosemont Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
1467	Co-trimoxazole 160mg/800mg tablets	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
15081	Ipral 100mg Tablet (E R Squibb and Sons Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary- tract Infections
59444	Co-trimoxazole 80mg/400mg tablets (Alliance Healthcare (Distribution) Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
53599	Trimethoprim 200mg tablets (Phoenix Healthcare Distribution Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
10318	Sulfamethoxazole 80mg with	Sulfamethoxazole	Sulphonamides And

	trimethoprim 16mg/5ml concentrate solution for infusion		Trimethoprim/Drugs For Pneumocystis Pneumonia
41579	Co-trimoxazole 80mg/400mg tablets (A A H Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
27445	Trimethoprim with sulfamethoxazole 160mg + 800mg/10ml Concentrate for solution for infusion	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
109	Septin Adult 80mg/400mg/5ml oral suspension (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
20920	Trimethoprim with sulfamethoxazole 80mg + 400mg/5ml Oral suspension	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
57080	Trimethoprim 100mg tablets (Waymade Healthcare Plc)	Trimethoprim	Sulphonamides And Trimethoprim
60808	Trimethoprim 50mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
1199	Co-trimoxazole 40mg/200mg/5ml oral suspension sugar free	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
27255	Trimethoprim 200mg tablets (A A H Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
477	Trimethoprim 50mg/5ml oral suspension sugar free	Trimethoprim	Sulphonamides And Trimethoprim
57642	Trimethoprim 20mg/5ml oral solution	Trimethoprim	Sulphonamides And Trimethoprim
56259	Trimethoprim 100mg tablets (Sigma Pharmaceuticals Plc)	Trimethoprim	Sulphonamides And Trimethoprim
57116	Trimethoprim 50mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Trimethoprim	Sulphonamides And Trimethoprim
54914	Co-trimoxazole 80mg/400mg tablets (Kent Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	Sulphonamides And Trimethoprim
45757	Trimethoprim with sulfamethoxazole 16mg + 80mg/ml Concentrate for solution for infusion	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
31227	Trimethoprim 200mg Tablet (Regent Laboratories Ltd)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
280	Monotrim 50mg/5ml Liquid (Solvay Healthcare)	Trimethoprim	Sulphonamides And Trimethoprim/Urinary-tract Infections
53720	Trimethoprim 100mg tablets (Almus Pharmaceuticals Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
36622	Monotrim 50mg/5ml oral suspension (Chemidex Pharma Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
21640	Trimopan 100mg tablets (Teva UK Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
25908	Sulfamethoxazole 800mg with trimethoprim 160mg tablet	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs

			For Pneumocystis Pneumonia
8286	Co-trimoxazole (trimethoprim and sulfamethoxazole) 80mg+400mg dispersible tablets	Sulfamethoxazole	Sulphonamides And Trimethoprim/Drugs For Pneumocystis Pneumonia
55986	Trimethoprim 200mg/5ml oral suspension	Trimethoprim	Sulphonamides And Trimethoprim
49592	Trimethoprim 100mg tablets (Phoenix Healthcare Distribution Ltd)	Trimethoprim	Sulphonamides And Trimethoprim
34633	Trimethoprim 200mg tablets (Sandoz Ltd)	Trimethoprim	Sulphonamides And Trimethoprim

APPENDIX 15 – Further details about covariates (extracted from ISAC Protocol 16_162R)

Covariates to be examined as listed in Chapter 5 (5.2.5 Data Management):

- age (years) at the time of index antibiotic prescription,
- sex,
- time of year (according to seasons: Dec-Feb = winter; Mar-May = spring; Jun-Aug = summer; Sept-Nov = autumn),
- RTI type (upper-, lower RTI, and otitis media),
- class of antibiotic (according to the BNFC classification),
- presence of one or more comorbidity,
- childhood vaccination status: diphtheria, tetanus, pertussis, polio and Hib (DTaP/IPV/Hib) and pneumococcal conjugate (PCV),
- social deprivation quintiles: based on patient-linked deprivation index score (IMD),
- number of previous “response failure” episodes during the 12-month period before the index prescription, and
- number of consultations for acute RTIs during the 12 months before the index prescription (baseline consultation rate).

Time of year (season)

There is a clear seasonal variation in antibiotic prescribing with a seasonal peak in winter months¹. Therefore “response failure” episodes are more likely to occur during winter (Dec-Feb = winter; Mar-May = spring; Jun-Aug = summer; Sept-Nov = autumn).

The number of previous “response failures”

Previous “response failure” will be defined as the number of “response failure” episodes in the 12 months before the index antibiotic prescription.

Class of antibiotic

For the purposes of this study, we will categorise antibiotic class according to the BNFC classification (Chapter 5.1).

Vaccination status

The immunisation schedule of childhood vaccinations in the UK is conducted according to age. The two most relevant vaccinations in children <5 years with RTIs are Diphtheria, tetanus, pertussis, polio and Hib (DTaP/IPV/Hib) and Pneumococcal conjugate (PCV). Influenza vaccination was only recently introduced to the immunisation schedule in 2012 and will not be a covariate. For the purposes of this study and specific to acute RTI, pneumococcal and haemophilus influenzae b vaccination status are of important.

Complete vaccination: a child will be presumed to have complete vaccination if the child had received an adequate number of immunisations to have had a protective immune response:

- (a) PCV vaccination ≥ 2 PCV before <12 months of age or at least 1 PCV dose after the age of 12 months
- (b) DTaP/IPV/Hib vaccination: 3 are required before <12 months or at least 1 DTaP/IPV/Hib dose after the age of 12 months

Incomplete vaccination:

(a) Children whose GP surgery notes do not contain any record of them having received the pneumococcal conjugate vaccination or *Haemophilus influenzae* b vaccination will be assumed not to have received these vaccinations.

(b) Children who received 0 or 1 PCV dose (< 12months of age) or do not fulfil criteria for complete DTaP/IPV/Hib vaccination will be considered as incompletely vaccinated.

Co-morbidity

We will adjust for the presence of one or more comorbidity as listed below. The list of potential comorbid conditions is based on recent criteria for children at risk of influenza complications and invasive pneumococcal disease ^{2,3}. These will be:

System	Condition
Respiratory	Asthma requiring continuous or repeated use of controller therapy (inhaled corticosteroids) Bronchopulmonary dysplasia Cystic fibrosis
Cardiac	Congenital heart disease Chronic heart failure
Neurological	Chronic neurological or neuromuscular disorder which compromises respiratory function (e.g. cerebral palsy)
Renal	Chronic kidney disease Nephrotic syndrome Kidney transplantation
Liver	Cirrhosis Biliary atresia Chronic hepatitis
Immunodeficiency	Asplenia or splenic dysfunction HIV infection Undergoing chemotherapy leading to immunosuppression Taking regular systemic steroids at a dose equivalent to prednisolone 20mg or more per day (any age) or ≥ 1 mg per kg per day (children under 20kg)
Other	Diabetes mellitus (type 1 or type 2) or other metabolic condition Genetic abnormality (e.g. Down's syndrome) Sickle cell disease Malignancy Prematurity (born before 37 weeks gestation) in children aged 12 to 23 months

References

¹ Holstiege J, Schink T, Molokhia M, et al. Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study. *BMC Pediatrics* 2014; 14: 174.

² Gill PJ, Ashdown HF, Wang K, et al. Identification of children at risk of influenza-related complications in primary and ambulatory care: a systematic review and meta-analysis. *The Lancet Respiratory medicine* 2015; 3(2): 139-49.

³ Yildirim I, Shea KM, Little BA, Silverio AL, Pelton SI. Vaccination, underlying comorbidities, and risk of invasive pneumococcal disease. *Pediatrics* 2015; 135(3): 495-503.

APPENDIX 16 – Secondary analysis: relationship between RTI-associated antibiotic exposure in the 12 months prior to index consultation and response failure criteria. Values are numbers of children.

	Response failure					
Antibiotic exposure	Referral	Second prescription	Emergency department visit	Hospital admission	Death	Total
None	645	834	274	106	1	1,860
1	390	508	97	34	0	1,029
≥ 2 antibiotic courses	324	415	55	26	0	820
Total	1,359 ^a	1,757 ^b	426 ^c	166 ^d	1 ^e	3,709

- a: Days to referral (median, IQR) = 2 days (0-8)
- b: Days to second prescription (median, IQR) = 9 days (6-12)
- c: Days to emergency visit (median, IQR) = 2 days (1-8)
- d: Days to hospital admission (median, IQR) = 3.5 days (1-9)
- e: Death occurred at day 5

APPENDIX 17 – Sensitivity analyses (primary analysis): the number children with a RTI-associated antibiotic prescription in the preceding 12 months excluding antibiotic prescriptions (a) within 14 days and (b) 56 days of the index prescription

(a) Excluding prescriptions within 14 days of index prescription					
Overall		Response Failure	No response failure	Adjusted Odds Ratio [95% CI]	P value
None	96,132 (84.08%)	1,070	95,062	1 [Reference]	
1	14,415 (12.61%)	217	14,198	1.00 [0.85-1.18]	p=0.98
≥ 2	3,782 (3.31%)	90	3,692	1.28 [1.01-1.61]	p=0.046
(b) Excluding prescriptions within 56 days of index prescription					
Overall		Response Failure	No response failure	Adjusted Odds Ratio [95% CI]	P value
None	98,862 (86.47%)	1,146	97,716	1 [Reference]	
1	12,547 (10.97%)	165	12,382	0.83 [0.69-0.98]	p=0.03
≥ 2	2,920 (2.55%)	66	2,854	1.13 [0.86-1.47]	p=0.38

APPENDIX 18 – Sensitivity analyses (primary analysis): the number children with a RTI-associated antibiotic prescription in the preceding 12 months excluding antibiotic courses for (a) children under one years old and (b) where the first criterion of our study outcome was used i.e. subsequent prescription within 14 days of the index antibiotic course)

(a) Excluding children under 1 years old at the time of index prescription (N=99,891)					
Overall		Response Failure	No response failure	Adjusted Odds Ratio [95% CI]	P value
None	81,770 (81.86%)	810	80,960	1 [Reference]	
1	14,208 (14.22%)	215	13,993	1.03 [0.87-1.22]	p=0.75
≥ 2	3,913 (3.92%)	95	3,818	1.29 [1.01-1.64]	p=0.04
(b) Excluding children where the first criterion of our study outcome was used (N=114,023)					
Overall		Response Failure	No response failure	Adjusted Odds Ratio [95% CI]	P value
None	95,115 (83.42%)	782	94,333	1 [Reference]	
1	14,897 (13.06%)	198	14,699	1.21 [1.02-1.44]	p=0.03
≥ 2	4,011 (3.52%)	91	3,920	1.54 [1.20-1.98]	p=0.001

APPENDIX 19 – Recruited GP practices in Oxfordshire Clinical Commissioning Group (CCG)

GP practices in the Oxfordshire CCG were selected based on their locality (urban vs semi-rural), level of social deprivation (index of multiple deprivation score and quintile group) and antibiotic prescriptions per practice list size as outlined in Chapter 6.

GP practice	Locality	IMD score by practice postcode ^{a,b}	IMD quintile group	Antibiotic prescriptions per practice list size ^c
Windrush Medical Practice, Witney, OX28 6JS	Semi-rural	15.25	3	Upper
The Leys Health Centre , Dunnock Way, Oxford, OX4 7EX	Urban	45.23	5	Upper
East Oxford Health Centre, 1 Manzil Way Oxford, Oxfordshire, OX4 1XD	Urban	21.66	4	Upper
Broadshires Health Centre, Carterton, OX18 1JA	Semi-rural	4.61	1	Middle
Summertown Health Centre, Summertown Oxford, OX2 7BS	Urban	10.87	2	Lower
27 Beaumont Street , Oxford OX1 2NR	Urban	20.37	3	Lower
King Edward St Medical Practice, Oxford OX1 4JA	Urban	20.37	3	Lower
Didcot Medical Centre, Didcot OX11 7JH	Semi-rural	9.97	2	Lower

^a IMD: index of multiple deprivation score

^b Classification of IMD score (quintile group, [IMD score range]): 1, [$\leq$ 8.49 (Least deprived)]; 2, [8.5 - 13.79], 3, [13.8 - 21.35]; 4, [21.36 - 34.17]; 5, [$\geq$ 34.18 (Most deprived)]

^c Antibiotic prescriptions per practice list size across Oxfordshire CCG subdivided into upper, middle and lower third (Public Health England <https://fingertips.phe.org.uk/profile/general-practice>)

APPENDIX 20 – Promotional study material for PAUSE Study (front and reverse)

Participants were provided with promotional written information about the study either by their health practitioner at participating GP practices or by the chief investigator at local baby/toddler groups as outlined in Chapter 6.



Antibiotic resistance

What does it mean for you and your family at home?



Has your preschool child experienced a recent respiratory tract infection (chest, ear or throat infection)?

University of Oxford researchers are undertaking a research study and would like to interview parents/carers to find out what you think is important when considering antibiotics for your young child with a respiratory tract infection.

To find out more please contact the research team directly:

www.phc.ox.ac.uk/pause

Chief Investigator:

Dr Oliver van Hecke, Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG.

Email: oliver.vanhecke@phc.ox.ac.uk

Tel.: 01865 617839



NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

Funded by



**National Institute for
Health Research**

Postcard Version 0.2, 20 September 2018. Parents' perceptions of Antibiotic USE and antibiotic resistance (PAUSE): a qualitative interview study
IRAS Project number: 194485. Dr Oliver van Hecke (Chief Investigator)

Poster in GP waiting rooms

Posters advertising the study were made available in participating GP waiting rooms

Antibiotic resistance

What does it mean for you
and your family at home?



Has your preschool child experienced a recent
respiratory tract infection (chest, ear or throat
infection)?

University of Oxford researchers are undertaking a research
study and would like to interview parents/carers to find out
what you think is important when considering antibiotics for
your young child with a respiratory tract infection.

To find out more please speak with your GP when you go in
for your consultation, or contact the research team directly:
www.phc.ox.ac.uk/pause

Chief Investigator: Dr Oliver van Hecke, Nuffield Department of Primary Care
Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford.
OX2 6GG. Email: oliver.vanhecke@phc.ox.ac.uk • Tel.: 01865 617839



NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

Funded by



**National Institute for
Health Research**

Poster Version 0.2, 20 September 2016. Parents' perceptions of Antibiotic Use and antibiotic resistance (PAUSE): a qualitative interview study, IRAS Project number: 194485. Dr Oliver van Hecke (Chief Investigator)

APPENDIX 21 – Participant information leaflet for PAUSE Study

What is the purpose of this research?

The main aim of the research is to find out what parents or carers think about antibiotics and antibiotic resistance.

We are interested in talking to parents and carers about occasions when a child in their care had a respiratory infection (e.g. chest, ear or throat infection) and what they did to help their child get better.

This educational study will provide information for other parents and carers and health care professionals about how parents manage children with respiratory infections and tell us how we can improve discussions about antibiotic use between health care professionals and patients.

Why have I been chosen?

We are inviting around 15-20 parents or carers of preschool children (6 months to 5 years) whose child had a *recent* respiratory tract infection (e.g. within 3 months). We would like to interview parents or carers whether or not they saw a doctor or nurse (e.g. GP/ walk-in centre/emergency department), and whether or not their child was prescribed an antibiotic.

What do I have to do?

The interview will be arranged at a time to suit you - at your home or other suitable setting of your choice, and will last between 45 and 60 minutes. Before starting the interview you will be asked to sign a form to confirm that you fully understand what taking part in the study will involve and that your questions about the research have been answered. You will be given as long as you need to decide whether to take part or not.

What are the advantages and disadvantages of taking part?

There are no direct advantages or disadvantages to you. We hope the information gained from this study will be used to give a voice to parents about their experiences of caring for their child when they are unwell, their decision to consult their health professional, and their beliefs about antibiotic use and antibiotic resistance.

Will my taking part in the study remain confidential?

With your permission the interview will be audio-recorded to make an accurate record of what is said and then the recording will be stored on a

secure computer and then typed up. This written record (transcript) will not include any names or other defining details that can identify you, to ensure confidentiality. The recording will be held in a locked cabinet in the University of Oxford to which only the research team will have access, until the end of the study when they will be deleted. So that we can speak to a wide range of parents, we will collect specific demographic details (your age, number of children in family, age and ethnicity of child). The transcript of your interview will be kept for 10 years following the end of the study. The findings from this study will be used in research reports but no names will be included in the report so any quotes from the interview will be anonymous.

What happens if I change my mind?

Taking part in this research is voluntary. It is up to you to decide whether to take part. If you decide not to take part in the study this will not affect the standard of care your child will receive in the future. You can withdraw yourself and your data without penalty at any time, up to the end of study and without giving a reason. If you withdraw from the study your data will be deleted from our records.

What happens if something goes wrong?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

If you wish to complain about any aspect of the way in which you have been approached or treated you should contact Dr Oliver Van Hecke or Dr Sarah Tonkin-Crine the senior investigator of the study (01865 617935, sarah.tonkin-crine@phc.ox.ac.uk). Alternatively, you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email: ctrg@admin.ox.ac.uk.

If you disclose any information that may cause harm to yourself or others, or relates to criminal activity then the researcher has a duty of care to report such information.

What will happen to the results of the research study?

The results will be published in scientific journals and the findings will form part of the chief investigator's PhD thesis. A summary of the findings will be sent to all participants who would like to see the results and the full report can be made available on request.

Will I be reimbursed for any expenses?

Taking part in this research is voluntary. You will not incur any additional expenses by taking part in this study. If you complete an interview with a member of the research team, you will receive a £20 gift voucher as a token of our appreciation.

Who is organising and funding this study and who has reviewed it?

This research is being organised by the Department of Primary Care Health Sciences, the University of Oxford and is being funded by the National Institute for Health Research. This study has been reviewed and received favourable opinion by (add REC Ref once approved).

Where can I get more information?

If you would like to take part in the study or if you have any further questions please do not hesitate to get in touch with Dr Oliver van Hecke using the contact details below.

Principal Investigator: Dr Oliver van Hecke, Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

Thank you for reading this information.

Please get in touch if you would like to take part by contacting the research team.



NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

NHS
*National Institute for
Health Research*



Antibiotic resistance: what does it mean for you and your family at home?

We'd like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please ask us.

Contact the research team:

Dr Oliver van Hecke
Department of Primary Care Health Sciences, University of Oxford

APPENDIX 22 – Parent/Carer Interview Guide for PAUSE Study

Research study: Parents' perceptions of Antibiotic USE and antibiotic resistance (PAUSE)

Investigators: Dr Oliver van Hecke, Dr Sarah Tonkin-Crine, Dr Kay Wang, Professor Chris Butler.

Ethics reference: Health Research Authority (reference 16/NW/0779)

Topics to be explored: Below is a list of questions to be discussed in this study. The work will remain flexible with respect to participants' agendas but we will cover the topics. It is common in semi-structured work to develop topics and questions as new ideas emerge from early data collection. Therefore, we may add new topics as the interviews progress and data collection continues. However, the key topic of parents' and carers' views and understanding about the role of antibiotics and the significance of antibiotic resistance when their young child has a respiratory tract infection, will remain the same.

Briefing:

- 1) Thank participant for agreeing to take part.
- 2) Introduce self.
- 3) This interview is for the PAUSE study. The aims were described in the participant information sheet. People differ in their understanding about the role of antibiotics when they or their family are unwell. There is actually very little information available about how parents consider the benefits and harms of antibiotics, specifically about the risk of antibiotic resistance. It's these differences that we'd like to hear about and we would value your unique perspective.
- 4) If at any time during the interview you do not wish to answer a question that's okay.
- 5) I would like to digitally record our conversation. The recording will be typed out, but everything you say will be anonymous. Your name and any names you mention, and any places you mention will be taken out, so that if someone read your interview they would not know who you are or where you work.
- 6) Your interview will remain confidential, unless (as discussed and outlined in the consent form) it is possible that you or someone else is at risk, but this will be discussed with you first.
- 7) If, at any stage, you wish to stop the audio recorder, please let me know.
- 8) Do you have any questions?

Note: Name of child will be used where indicated by [child].

SECTION A

1. Tell me about the last time [child] was unwell (poorly) with a respiratory tract infection (e.g. chest, ear or throat infection) and what you did to help him/her get better.

2. Can you tell me about how [child] had been feeling and the symptoms that he/she had?

Prompts: How long had he/she had symptoms for? Why do you think they got ill? What did you think caused the illness? What were you most worried about?

3. What did you (or anyone else do) initially to try to help [child] get better?

Prompts: What did you do at home to help [child]? What medicines did [child] take? Who gave you advice about how to look after [child]?

4. Were you worried about that it might be something more serious?**

(**added after interview 2)

Prompts: Were you worried about sepsis?

5. What (other) sources of advice did you use to help you take care of [child]?

Prompts: Who did you speak to about how to care for your child? What information did you look up and where did you find this?

6. Did you visit a healthcare provider to get advice about [child's] infection?

If **YES**, why did you decide to visit the GP/ OOH service/ Accident & Emergency?*** What were you most concerned about? [then go to 8]

(**added after interview 4)

If **NO**, why did you decide not to visit the GP or other health care service? [then go to 7]

7. Can you tell me about any other time you have been to see a doctor or nurse about a similar illness for your child? [then go to section B]

Prompts: What advice did they give you? What did you think of the advice that you got?

8. What happened when you took [child] to see the doctor or nurse?

Prompts: How did you expect the doctor (or nurse) to help [child]? How did you feel about the advice they gave you? What did you think about the treatment they recommended?

9. Was [child] prescribed antibiotics by any healthcare professional during their visit?

Prompts: Did you expect an antibiotic to be prescribed by the doctor or nurse? Did you think [child] needed an antibiotic?

If prescribed an antibiotic, how did you feel about [child] being prescribed an antibiotic?

If not prescribed an antibiotic, how did you feel about [child] not being prescribed an antibiotic?

SECTION B

I'd now like to ask you a few questions about antibiotics.

10. Can you tell me a little bit of what you know about antibiotics in general?

Prompts: What have you heard about antibiotics?

What illnesses do you think they can help treat? How do you think antibiotics work?

11. Where did you hear that one needs to complete an antibiotic course?**

(**added after interview 2)

Prompts: Do you think completing an antibiotic course is important?

12. What sort of symptoms do you think need an antibiotic when you are unwell?

Prompts: Why did you think those symptoms need an antibiotic?

13. What sort of symptoms do you think need an antibiotic when [child] is unwell?

Prompts: Why did you think those symptoms need an antibiotic?

14. How do you feel about [child] taking antibiotics?

Prompts: What benefits do you think there are to taking antibiotics? What concerns do you have about [child] taking antibiotics?

15. Can you tell me about possible harms or side effects that people can experience if they take antibiotics?

Prompts: What risks do you think there are when taking antibiotics?

16. Tell me a little about what you know about “antibiotic resistance”.

Prompts: Where did you hear about it? Where would you get information about antibiotic resistance?

17. Tell me what you understand about the risk of antibiotic resistance for human beings.

Prompts: How do you think antibiotic resistance comes about? In what way do you think antibiotic resistance is harmful?

18. If we focus on you for a moment, how do you think antibiotic resistance is likely to affect your personal health?

Prompts: Do you think that antibiotic resistance is likely to affect you?

19. Now, let’s focus on your family and [child]. How do you think antibiotic resistance is likely to affect [child’s] health?

Prompts: Do you think there is any difference between how antibiotic resistance is likely to affect your family compared to other parents?

Section C

Now I’d like to show you a few examples about making people more aware about antibiotic resistance in the UK.

At this point participants will be shown two examples of antibiotic public campaigns in order to facilitate discussion and elicit participants' views about antibiotic resistance (see Appendix): Antibiotic Guardian and/or video clip from Dr Sally Davies
<https://www.gov.uk/government/news/countrys-most-recognisable-doctors-explain-antibiotic-resistance>.

20. How do these materials make you feel?

Prompts: What do you think about these leaflets or message? Is there anything new here, or that you haven't heard before? What surprises you about this information?

21. How would you change these materials to make them better?

Prompts: What would you want these materials to say? What would make you take notice of them?

22. Is there anything you personally can do to reduce antibiotic resistance?

Prompts: Do you think there is any connection between resistant bugs and the antibiotics [child] swallows? How do you think the antibiotic medicine you take relates to antibiotic resistance?

23. What have you heard about resistant bugs or infections?

Prompts: Have you had any personal experience of the effects of having a "resistant bug"? What have you heard about "superbugs" or MRSA for example?

24. We know that antibiotic resistance is harmful because too many antibiotics are used when they probably should not have been. But using fewer antibiotics might also mean that our body needs to fight off simple infections on its own. What do you think?

Prompts: What sort of symptoms would you be happy putting up with if it would minimise the chances of antibiotic resistance? What about coughing for longer? What about earache? What sort of (RTI) symptoms would you be happy [child] having if it would minimise the chances of them developing antibiotic resistance?

25. What would you as a parent/carer like to hear on how to minimise/reduce antibiotic resistance?

Prompts: How do you think we could improve messages about the risks and benefits of using antibiotics?

Closing question

Is there anything else that I haven't asked but that you would like to tell me? Thank you for taking the time today to help our research.

Additional Information: participant (mother/father or carer); age of parent; age of child; number of children in the family; ethnicity

Appendix

Examples of public antibiotic awareness campaigns or messages

1. Antibiotic Guardian leaflet and/or 2 minute Dr Chris van Tulleken video clip on <http://antibioticguardian.com/> website which is freely available and developed by Public Health England

Antibiotic resistance in numbers

25k The number of people who die each year across Europe from infections resistant to antibiotics

A recent study showed that the likelihood of GPs prescribing antibiotics for coughs & colds increased by 40% between 1999-2011

30 years The period of time since a new class of antibiotics was last introduced despite the fact that growing numbers of infections are resistant to antibiotics

40% Research has shown that only 10% of sore throats and 20% of acute sinusitis benefit from antibiotic treatment but the prescription rates are much higher than this

10%

€1.5 billion Annual EU wide cost of healthcare expenses and lost productivity due to antibiotic resistant bacteria

Public Health England

European Antibiotic Awareness Day (EAAD) is a Europe-wide initiative that takes place annually on 18 November.

Public Health England (PHE) is leading the co-ordination of EAAD activities in England in collaboration with Department for Environment, Food and Rural Affairs (DEFRA), the Department of Health, devolved administrations including Public Health Wales, and other professional organisations.

PHE have established the Antibiotic Guardian campaign to help protect antibiotics and improve knowledge about antibiotic resistance.

You are invited to become an Antibiotic Guardian

As an Antibiotic Guardian, encourage others to join you in protecting antibiotics against the growing threat of antibiotic resistance at www.publichealthwales.org/antibiotic-guardian

lechydd Cyhoeddus Cymru
Public Health Wales

Protect yourself, your family and friends against the spread of antibiotic resistance.

Become an

ANTIBIOTIC GUARDIAN

www.publichealthwales.org/antibiotic-guardian

What is antibiotic resistance?

THE PROBLEM

Antibiotics treat infections by killing bacteria, but now the bacteria are fighting back. Our medicines are becoming less effective which means more deaths and more complications for people receiving treatment in hospital. We have to tackle this problem before it gets worse.

HOW THIS HAPPENED

There are many reasons why antibiotics lose their effectiveness, but here are two key ones:

Firstly, we take medicines that we don't need. Antibiotics don't help most colds or coughs get better but we still request antibiotics for them.

Secondly, we make things worse when we don't take antibiotics exactly as prescribed for instance, missing doses. Never save antibiotics for future use or give them to someone else.

WHAT CAN WE DO?

Antibiotic resistance is one of the biggest threats facing us today but you can help. Please visit www.antibioticguardian.com and find out about simple steps you can take to save our antibiotics.

A world without antibiotics

PRE-ANTIBIOTIC AGE

In a world before antibiotics, as recently as the 1930s, people often died from infections like pneumonia or meningitis. Simple medical procedures/operations were risky due to the chance of infection. Antibiotics changed that.

ANTIBIOTIC AGE

Since the 1940s our antibiotics have allowed us to fight infections and save millions of lives. But they are becoming ineffective against many infections because we aren't using them properly.

POST-ANTIBIOTIC AGE

If bacteria become 'resistant' to our antibiotics many routine treatments will again become increasingly dangerous. Setting broken bones, basic operations, even chemotherapy all rely on access to antibiotics that work. Antibiotic resistance is one of the biggest threats facing us today but we have a chance to fight back. Find out how at: www.antibioticguardian.com

Antibiotic resistance What can I do?

BE AN ANTIBIOTIC GUARDIAN

Antibiotics are some of our most precious medicines, used to treat both humans and animals. The Antibiotic Guardian campaign was launched to kick-start collective action from both healthcare professionals and members of the public to work together to slow the spread of antibiotic resistance.

By pledging to become an Antibiotic Guardian you choose to perform a simple action which protects antibiotics against the threat of antibiotic resistance.

TAKE THESE SIMPLE ACTIONS

- Don't ask for antibiotics, treat your cold and flu symptoms with pharmacist advice and over the counter medicines
- Take antibiotic exactly as prescribed, never save them for later, never share them with others
- Spread the word, tell your friends and family about antibiotic resistance

SIGN UP AND LEARN MORE

Rally together at antibioticguardian.com and choose a pledge that feels right for you. Remember that your actions protect antibiotics.

2. Four minute video clip of Chief Medical Officer, Dr Sally Davies <https://www.gov.uk/government/news/countrys-most-recognisable-doctors-explain-antibiotic-resistance>

APPENDIX 23 – Consent Form for PAUSE Study

Parents' perceptions of Antibiotic USE and antibiotic resistance (PAUSE)

Parent/Carer Interviews

Chief Investigator: Oliver van Hecke

Address: Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford

Email: oliver.vanhecke@phc.ox.ac.uk, Telephone: 01865 617 839

Participant Study ID:

If you are happy to take part in this research then please read all 6 statements below and initial the boxes if you agree with them.

**Please initial
each box**

1. I confirm that I have read and understand the participant information sheet version [v1.0, dated 6 October 2016] and that I have had the opportunity to ask questions and had them answered satisfactorily.
2. I agree to take part in this research study and understand that all my details will be kept confidential, that no personal information will appear on any reports or documents and only a unique ID number will be used.
3. I understand that the interview will be audio-recorded and no one but the research team and an independent transcriptionist will hear the recording.
4. I understand that my participation is voluntary and that I am free to withdraw at any stage without giving reasons and without my legal rights being affected.
5. I give permission for anonymous quotes from the interview to be included in reports of the findings from the research.
6. I understand that data collected during the study may be looked at by individuals from the University of Oxford, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research.

☐☐☐☐☐☐

Name of Participant

Signature

Date

Name of Person taking Consent

Signature

Date

1 copy for participant; 1 copy for research team.

APPENDIX 24 – Coding framework with candidate themes and subthemes

This table presents the coding framework developed after analysis of 10 interviews showing the initial themes and subthemes by which remaining interview transcripts were coded. Themes and subthemes were amended and refined according to later interviews. The final themes and subthemes are presented in Table 2 of Chapter 6.

Theme 1 Parents' experiences of managing RTIs in their children

A. Parental concern regarding child's symptoms

Child has several symptoms and was uncomfortable
Nature of child's illness (symptoms)
Symptoms usually not attributable to specific virus or bug
Green phlegm indicates bacterial infection
Atypical symptoms worry parents
Any infection is potentially also bacterial infection
Cold symptoms lasted 1.5 weeks as expected
Duration of illness was a concern because of disruption, not fear of serious illness
Parents not worried about symptoms
Parents struggle to let their own child suffer with the same infection symptoms
Parents trust their gut instinct when their child is ill
Parents worried about serious infections
Parents worried that child may deteriorate and become emergency
Symptoms that parents would be happy to put up with
Symptom is persistent after 2 days
Symptoms that made parents worry more
Some infections are hidden and need expert advice
Most RTIs are caused by viruses
Wary that certain serious infections we cannot fight on our own
Children prone to getting frequent minor illnesses
Parents want to avoid hospital admission
Guilt associated with missing opportunity to seek medical advice

B. Parents' sources of advice and treatment strategies at home

Parents put up with child's RTI symptoms for 4-5 days (except pain)
Putting up with symptoms of your child is different because they're so young
Parents would be prepared to put up with symptoms for themselves (except pain)
Put up with these symptoms without antibiotics in adults and also children
Parents' sources of information for advice, and help for caring for their sick child
Personal experiences of other parents on internet more useful than scientific evidence
Parent's treatment strategies at home

Theme 2 Parents' experiences of consulting the GP for treatment

A. Parents' decision about consulting their GP

Decision to contact GP
Parents attend GP for reassurance and a plan, not necessarily antibiotics
Parents had different ideas about when to consult
Parents keen to have early intervention for their child
Parents use internet to check up on or challenge GP decisions
Parents want to know that their child will be fine without antibiotic
Placing your trust in GP when child unwell

Parents want the best and quickest treatment necessary for the care of a child
Clinician expert needs to assess unwell child for parental reassurance
Would not go to GP quickly, would always wait a few days
Decision to consult GP advised by nursery
Parents less inclined to contact GP now unless symptoms unusual

B. Perceptions of GP management and access to healthcare

Diagnostic evaluation by GP or other healthcare provider
Challenging GP authority might put child's life in danger
Consultation experience with healthcare provider
Treatment strategies offered by GP or healthcare provider
Access to healthcare provider is available and essential
Couldn't get to a GP soon when child was unwell

C. Perceived appropriateness of antibiotics at GP/hospital

C (1) Parents' expectations for antibiotics (in general)

Expectation for antibiotic is based on past experience of parents
Only want child to take antibiotics if necessary
If child had to take antibiotics, parents would allow
Poorer people request more antibiotics because of their lower education level attainment
Preference for GPs to be direct, address parent's agenda for antibiotics
Parents seeking antibiotics will see another GP, NHS 111 or out of hours
Media stories say public rely on antibiotics and GPs ought to prescribe less
Too many antibiotics are prescribed in primary care
Parents that do not understand AMR might not accept "no antibiotics"
Patients trust GPs judgement about when antibiotics are needed
Antibiotics needed for something more extreme or causing discomfort rather than just common infection

C (2) Parents' expectations for antibiotics for their unwell child

Expectation for antibiotics is not automatic, but atypical symptoms worry parents
Happy that child was prescribed an antibiotic just in case
Happy with GP explanation no antibiotic was needed (for child)
Hesitant to use antibiotics for her child
Conflict between trusting GP, and whether it is truly the correct thing to prescribe antibiotics
Parent felt emotionally unable to question the need or reason for child's antibiotic
Parent did not expect antibiotic as she couldn't tell if it was viral or bacterial
Parent happier for antibiotics if bacterial infection is confirmed
Parent happy that GP didn't approach the topic of antibiotics
Parent not keen that child has frequent antibiotics
Parent not wanting child to be dependent on antibiotics
Parent resist taking an antibiotic for as long as possible for themselves
Parent unhappy that child is on antibiotics
Parent would prefer to have discussion with GP about antibiotics for their child
Parents expectation for antibiotics
Parents reluctant that child has more than 2 courses per year
Questions parents would have liked to ask the GP when prescribing antibiotics
Wished they'd ask more questions about antibiotic from the GP
Child prescribed antibiotic but not given
Uneasiness about antibiotics being used too often, too readily
Worry that there is underlying reason for so many antibiotics
Some parents will motivate reasons for antibiotics through their own online research
Happier to use alternatives to antibiotics for children if possible

D. Perceptions of the role of antibiotics in family life

- Antibiotics allow children to attend nursery
- Antibiotics viewed as a quick fix
- Psychological dependence or crutch of antibiotics
- Child's illness potential disruption to travel, family life
- Unwell child affects the whole family
- Less tolerance for illness in society
- Nursery requires attendance at GP before child return
- Pill popping culture of modern lifestyle in the Western world
- Pressure from employers to return to work after 1 week of acute illness
- Take antibiotics to get back to work more speedily
- Self-treating has become less popular because of more knowledgeable public
- No alternatives to antibiotics

Theme 3 Uncertainty about the risks of antibiotics and their use

A. Perceptions of harms of antibiotics

- Parent wary of antibiotics
- Allergic reaction is a potential harm of antibiotics
- Antimicrobial resistance (AMR) is potential harm of using antibiotics
- Antibiotics encourage resistant bacteria
- Antibiotics have been tested, so are not risky for children
- Antibiotics linked to chronic conditions like asthma, eczema and changing the gut flora
- Experienced GI upset as antibiotic side-effect
- Inherent risks of taking any medication
- Risks of antibiotics have been downplayed or not common knowledge
- Some antibiotics can give GI irritation
- Unclear about the risk of antibiotics and antibiotic resistance
- Unsure about risks associated with antibiotics
- The harms of antibiotics are poorly understood
- Unsure of how antibiotics may affect health in adults
- Antibiotics are risky for pregnant mothers
- Antibiotics kill off the good bacteria is concerning
- Concerns if child has numerous antibiotics in a year
- Long-term consequences of antibiotics in young children remain unknown
- Not aware of side-effects or other risks of antibiotics
- Taking too many antibiotics weakens the immune system
- Taking too many antibiotics decreases the effectiveness of antibiotics
- Too many antibiotics prescribed will lead to children catching infections more easily
- Without antibiotics better for child's overall health and boost immunity
- Supplements like yoghurt needed for child on antibiotics
- Parents view antibiotic harms differently for themselves and their children
- Antibiotics can shut down bodily organs
- False public perceptions that drugs (antibiotic) can help anything
- Unaware that multiple antibiotic courses in children may have consequences

B. Perceptions and experiences of benefits of antibiotics

- Child got better after taking antibiotics
- Child recovered quickly on antibiotics
- Child recovered without antibiotics
- Grateful that child responded to antibiotics
- Some people cannot afford to be ill, and antibiotics work
- Child needed antibiotic when newborn for serious infection
- Child prescribed antibiotic for tonsillitis in the past
- In the past, sore throats needed antibiotics
- Parents' personal (past) experience with infection and antibiotics
- Parent's personal health has affected perceptions of antibiotics

Antibiotics help the immune system
Antibiotics prevent infections becoming more severe
Antibiotics to prevent severe infections are cost-efficient
Antibiotics given for infections

C. Perceptions of how and when antibiotics ought to be used

C (1) Symptom severity and duration

Antibiotics are need occasionally for severe symptoms
Antibiotics speed up the recovery, reduce the duration of symptoms
Antibiotics used for symptoms that carry on for too long
Antibiotics help the body to recover quickly
Need for antibiotic depends on severity and duration of illness
Antibiotics are needed for serious or certain illnesses
Antibiotics needed for conditions that don't get better on their own
Expectation for antibiotics for their child for something more extreme or causing discomfort

C (2) Symptoms associated with infections

Cough associated with fever might need an antibiotic
Cough associated with unusual symptoms might need an antibiotic
Fever may be a sign of infection, but not indication for antibiotic
Green phlegm in child might need an antibiotic
Greater likelihood of antibiotics if productive cough and out of breath than flu-like illness
Parents unsure what sort of symptoms might need an antibiotic
The sort of symptoms that might need antibiotic are the same for adult or child
Unsure whether antibiotics help to clear up specific symptoms
Ideas about what symptoms antibiotic are used to treat (in general)
Pain and fever symptoms need an antibiotic

C (3) Specific named infections or conditions

Antibiotics needed for chest infections
Not all chest infections need an antibiotic
Antibiotics also used for nasty infections like sepsis, meningitis
Antibiotics necessary for skin or wound infections
Antibiotics needed for earache; persistent fever in children
Diarrhoea (gastroenteritis) might need an antibiotic
Ear infections need antibiotics in children
Parents unaware that only a small proportion of sinusitis or sore throat might benefit from antibiotics
Most RTIs do not need an antibiotic
Parent unsure for conditions antibiotics should be prescribed
Sore throat normally does not need antibiotic
Would consider antibiotic for persistent chest infection
Antibiotics used for infections after operations

C (4) Perceptions of how antibiotics are used

Antibiotic do not speed recovery for non-bacterial infections
Antibiotics are so frequently prescribed both when they are needed, and not
Antibiotics have been prescribed unnecessarily to some people
Antibiotics only effective against bacteria
Comparison of using antibiotics for infections with peptic ulcers
If a child is in pain something is needed to stop it
Specific antibiotics target specific bacteria
Using antibiotics once, or having a large interval between taking antibiotics is acceptable
Parents pressured by family members, or previous generation to use antibiotic more often

Antibiotic warranted when child is very young
Antibiotics were needed in hospital for a viral infection
Unaware that antibiotics are used beyond infections

C (5) Perceived need to complete antibiotic regimes

Antibiotics need to be taken for 1 week
Antibiotics should be completed even though child is better
Antibiotic regimes are difficult to follow with children
Completed antibiotic course statement
GPs and pharmacists advise to complete antibiotic course
People are not finishing antibiotic courses or as prescribed
Sought information about antibiotics on medicine leaflet

Theme 4 Parents' understanding of AMR
--

A. Description and knowledge of AMR

Antibiotic resistance is when a person does not respond to antibiotics
Antibiotics stopped working against some strains of bacteria
Bacteria become resistant because of antibiotic overuse
Bacteria learn to resist the effects of antibiotics
Definite link between resistant bacteria and antibiotic resistance
Humans become resistant to antibiotics
Individual develops resistant bacteria "to the (antibiotic) drug"
Personal little knowledge about antibiotic resistance
Resistant bacteria share their DNA with other bacteria
Unable to recall what antibiotic resistance is
Unaware that antibiotic resistance is a potential harm of using antibiotics
People can carry and transmit resistant bacteria to children
Pets can also harbour bacteria
AMR will affect the ecology/environment long-term
First time antibiotic resistance highlighted was MRSA scare
Potential for AMR to be catastrophic, but some would survive
Public more aware of the AMR risk than previously
There is a lot of antibiotic resistance at a population level
There's a point in the future where antibiotic cannot help
Different cultures have differing attitudes towards antibiotic
Recognising that changing a culture is difficult
New antibiotics are not being developed
Antibiotics overused a lot in hospitals
Antibiotic resistance is caused by mutating bacteria
Mutating resistant bacteria are unstoppable

B. AMR associated with frequent antibiotic use and inappropriate behaviours

Antibiotics that are misprescribed brings about AMR
Antibiotic resistance occurs when people are prescribed antibiotics regularly
Antibiotics used for non-bacterial infections cause resistance
Greater antibiotic exposure makes AMR more likely
Not completing antibiotic course promotes AMR
Not finishing antibiotic courses increases AMR
Residual bacteria after antibiotic use result in antibiotic resistance
Resistance occurs because of antibiotic overuse
Using household antibacterial products promotes antibiotic resistance
Antibiotics are not solely to blame for antibiotic resistance
Using no antibiotics unless you have to reduces AMR

C. Sources of information about AMR

Internet search engines are better sources of information about AMR than NHS website
Medical journal might also be an information source about AMR
Self-reading as source of information about antibiotic resistance
TV programme information source about antibiotics and AMR
Most people would turn to their GP for advice about AMR
People should be better informed through GPs about AMR
News about AMR does not worry parents
News media and family members are a source of information about antibiotic resistance
NHS site trustworthy for information about antibiotic resistance
Scientific magazine as a source of information about AMR
Sites like Mumsnet less trustworthy
Sources about AMR from moms' chat groups

Theme 5 Perceived consequences of AMR

A. Implications for patients

AMR will make recovery from infections longer
AMR will put certain patient groups (chronic health problems, young, old) at risk of serious illness, sepsis
Antibiotic resistant infections can be more severe
Antibiotic resistant infections have serious consequences
In the future we'll not have the means to fight off infections
Initially humans will be sicker but will overcome because of an adaptable immunity
Less developed immune system more at risk of AMR
Resistance will make humans vulnerable to bacteria an infection
Resistant bacteria might affect the body's natural immunity to cope
Simple infections will not be cured and people will suffer more, die
Antibiotics not working might have serious consequences
Without antibiotics, humans would fight infections themselves
Travelling to countries with high AMR is risky
Patients in hospital are at greatest risk of the effects of antibiotic resistance

B. Impact of AMR on close family

AMR will affect younger children more than the parents
Antibiotic resistance is likely to affect everyone the same incl. children
Antibiotic resistance will affect children similarly to adults
Other people not responding to antibiotics is not likely to affect family
Poorer people might be more affected by antibiotic resistance
Resistant bacteria can be transferred between humans
Risk of antibiotic resistance has a future impact for her child's health
Family less likely to be affected because they hardly ever use antibiotics
Family low risk of antibiotic resistance because less focussed on hygiene
Antibiotic resistance is unlikely to affect current generation

C. Healthcare implications (cost)

AMR means using costly 3rd or 4th line antibiotics
Antibiotic resistance might make future courses of antibiotic ineffective
Antibiotic resistance might need further interventions to treat infection
Resistant bacteria may affect routine hospital procedures
Resistant bacteria will mean that new antibiotics won't work
Resistant infections might impact on health services, waiting times for an appointment
AMR makes bacteria stronger
Resistant bacteria present a wider health problem

D. Unknown implications

Long-term effect of resistant bacteria unknown
 Aware that antibiotics aren't working as before but not linking this to antibiotic resistance
 Prospect of antibiotics that are ineffective is scary for some people
 Unsure what the relevance of antibiotic resistance is for the human race
 Antibiotic resistance is a problem for the future
 Concept of AMR is abstract but remains a possibility
 Doom and gloom associated with AMR
 The risk of antibiotic resistance is small
 Greater antibiotic doses make the risk of AMR more likely

Theme 6 Ways to reduce antimicrobial /antibiotic resistance (AMR)

A. Healthy lifestyle choices to reduce AMR

Chemicals and hormones in food are a vicious circle
 Goals to reduce AMR are achievable and simple
 Staying healthy will be protective against AMR
 Taking responsibility for own health to reduce need for antibiotic
 The immune system can learn to combat resistant bacteria
 Try to eat more healthily to help antibiotic resistance
 Boosting your immune system through vaccination
 Changing lifestyle through healthy diet and exercise can reduce reliance on antibiotics
 Eating better, less processed food can reduce antibiotic resistance
 Exposure to bacteria (bugs) improves boosts your immune system
 Less household anti-septic products can reduce antibiotic resistance
 People need to take responsibility for their own health
 Staying healthy reduces the frequency of antibiotics
 Vaccination helps against certain illnesses e.g. mumps

B. Prudent use of antibiotics and advice about non-antibiotic strategies

Completing antibiotic courses reduces the risk of AMR
 Feel unable to reduce antibiotic resistance themselves as it's much bigger
 Is there more than using less antibiotics to reduce AMR
 Aware not to ask for, or share antibiotics
 Children are made healthier if exposed to infections without antibiotics
 Low users of antibiotics are unlikely to be affected by antibiotic resistance
 Parents delay taking antibiotics for as long as possible to reduce AMR
 Save antibiotics for when you really need them
 Access to advice from GPs, nurses or health visitors
 "Not doing much" to reduce antibiotic resistance
 Collective public effort is needed to use fewer antibiotics

Theme 7 Parents' reflections on current antibiotic awareness materials

A. Perceived personal relevance of campaigns

Leaflet 1 (Antibiotic Guardian) never seen before
 What is an antibiotic guardian
 Leaflet 1 does not state explicitly that there is antibiotic resistance
 Leaflet 1 title not enticing compared to Leaflet 2
 Leaflet 2 informative about infection transmission, and prevention
 Leaflet 2 more information about the implications of antibiotic overuse
 Positive points about Antibiotic Guardian Leaflet
 Push to see people would understand meaning behind poster (Leaflet 2)
 Numbers on AMR were shocking
 Parents surprised that GP antibiotic prescribing increased or so high

- Parents surprised that no new class of antibiotics discovered
- Parents unaware that antibiotics are used beyond infections
- Surprised at the healthcare related cost of AMR
- Surprised at the loss of productivity cost because of AMR
- Surprised that overuse of antibiotics is one of the main reasons for AMR
- Surprised that people do not complete the antibiotic course
- Surprised that so many people across Europe die each year from resistant infections
- Unaware that saving antibiotics at home is not recommended
- Aware that not a great percentage of sore throats benefit from antibiotics
- Leaflet 2 could be misinterpreted that antibiotics are not allowed for flu-like illness

B. Perceptions of enablement

- Antibiotic Guardian leaflet potential for spreading awareness
- Leaflet 1 is not clear what individual persons can do themselves
- Leaflet 2 tells people not to resort to antibiotics, but doesn't say how
- Scaremongering in leaflets not welcomed
- Referring to a website to find out what to do was unwelcomed
- Suggestions for improving Get Well Soon leaflet
- Suggestions to improve Leaflet 1
- Wouldn't change Antibiotic Guardian leaflet except name perhaps
- Antithesis between getting better without antibiotics, and people dying without them
- Intrigued that people can fight back against AMR
- Happy that we fight certain infections on our own
- Happy with coughs that persist, flu-like illness without antibiotics
- Might be better not to take antibiotic but might be only cure
- Parents can deal with certain infections like chicken pox without seeing their GP
- Parents happy to avoid antibiotics dependent on child's symptoms, duration and severity
- The threshold for antibiotic treatment has to be lower for those at higher risk e.g. elderly and young

Theme 8 Social responsibility to inform parents about AMR

A. Better communication about antibiotics and AMR during clinical consultations

- Better communication needed between GP and parent about treatment strategy options
- GPs giving information about AMR during visits when not prescribing antibiotics
- GPs should explain why antibiotics were prescribed
- GP are time pressured in NHS
- GP uses antibiotic prescription as a hand out but might not be the right thing to do
- GPs aware of AMR but nothing out in place to curb overprescribing
- GPs don't have the time to tell people about AMR
- GPs feel pressured to prescribe more antibiotics (to poorer people)
- GPs know more about antibiotic resistance than the general public
- GPs need better tools to distinguish infections
- GPs not getting message about too much antibiotic prescribing
- GPs now are less inclined to prescribe antibiotics
- GPs under pressure may prescribe just to be safe
- Drive for GPs to reduce antibiotic prescribing
- Parents need to place their trust in GPs and nurses to make the correct decision
- GPs and nurses need to stick to their guns
- More appropriate use of the NHS by taking responsibility for their own health

B. Better public strategies

B (1) Challenges that future AMR strategies should address

- Changing people's awareness much easier and transient than changing behaviour
- Cultural issues around antibiotics and cleanliness need to be addressed
- Might take a generation to change a mindset about antibiotics

- Recognising that changing a culture is difficult
- Don't want to know more information about antibiotic risks
- Influence of antibiotics in animals not covered
- Public health messages that scare people might be useful
- Self-interests of individuals do not benefit society
- Point out that AMR is getting worse
- Research into why GPs are still prescribing antibiotics of questionable benefit
- Antibiotic use in animals also needs to be tackled

B (2) General comments to improve campaign messages

- Clearer websites explaining to people what to do
- State what people can do within the leaflet, and not website
- Diagrams might improve campaign messages
- GPs must be behind AMR campaigns
- Leaflet advice should link to what people do, not just a website
- More personalised messages can improve campaigns
- Visual warning about antibiotics
- Listing indications for antibiotics in numbers
- Target people about antibiotic stewardship in a context outside illness

B (3) Campaign messages aimed at parents

- Campaign messages need to reach parents
- Every child under 5 gets the same advice ie universal message
- Focus on younger generation or children to improve campaigns
- Messages aimed at families can improve campaigns
- Leaflet more direct (future) implications for children
- Leaflet more specific to individuals and family (children)
- Target parents that go see their GP for antibiotics
- Parents want to have information about antibiotics at hand at GP visit
- More information about how to manage symptoms at home
- Non-antibiotic strategies would be a solution
- Using alternative to antibiotics for milder infections
- Refocus strategy on immune system rather than infection, antibiotic
- Want to see more information about individual danger or risk
- Would like to know when antibiotics should be taken, and when not
- Address parents' concerns of the "worst case scenario"
- First-time parents worry more than parents with more children
- Empower children to educate their parents

B (4) Improved dissemination

- Face-face information at Science fairs
- E-bug leaflet aligned with teaching at school
- Website should contain all information but alternative should exist
- Playgroups, NCTs and child centres also good point of contact for dissemination
- Same simple message needs to be disseminated across entire country
- Various strategies needed to get message across about AMR
- Television and radio adverts disseminating information
- TV not watched regularly
- Other routes such NHS 111 or pharmacists
- Health message about antibiotics through new baby/health visitor visits
- Social media might be easier but unclear whether it is effective

APPENDIX 25 – Coding manual with examples of typical quotes by theme, subtheme and description

Theme 1. Parents' experiences of managing RTIs in their children		
Subtheme	Description	Example quotes
Parental concern regarding child's symptoms	Parents describing their child's illness and their interpretations of specific symptoms.	<i>"He did [have fever]. He was ... It wasn't a high temperature. It was kind of 38-ish. 38.5. Which, we thought, "Oh, stick some Calpol in him, he'll be fine." (Participant #19)</i>
		<i>"Most worried about him going so downhill that it got ... it would be, like, an A&E situation or a 111 situation. I think I'm quite a patient and calm person and, you know, I try to keep a logical head about stuff but before having kids I would probably have said that more so, but when you're in the moment of your child, you know, lying on you and just being pale as a ghost and, you know, just being so lethargic. I was in tears when I phoned the GP so you just reach a point where I think your heart overrules your head a bit when it comes to, kind of, medicine and getting better." (Participant #4)</i>
Parents' sources of advice and treatment strategies at home	Parents' describing the sources of advice accessed when caring for their child at home and the strategies they used.	<i>"My mother-in-law lives with us so she, having had two daughters, we sought her advice. Well my wife eventually sought her advice after the Calpol's six hours or four hours expiring. And that helped. So, I was slightly surprised they hadn't gone to the GP sooner but they did eventually." (Participant #7)</i>
		<i>"Sometimes I will Google and go to sites like Mumsnet and look at people's discussions. I don't add to them but they're sometimes quite useful just to have a run over, as long as you've got a critical eye to people that are being over-anxious. So, although, there can be a worry that these discussion sites just egg people on to worry more, I think actually, often, you can find quite useful stuff because it's just people's experiences. So then you find out whether they've gone to the doctor or not, what the doctor did and it's quite helpful to get that history. And most of the time, actually, people are fairly reasonable on those kind of discussions." (Participant #17)</i>
		<i>"Generally, Calpol, Ibuprofen. [...] And just, kind of, keeping the temperature down and trying to keep her happy and not giving milk before bed, kind of, opting for clear fluids and, kind of, making sure she's had enough food but also enough time so that Calpol doesn't trigger her off being sick and things like that." (Participant #2)</i>

Theme 2. Parents' experiences of consulting the GP for treatment		
Subtheme	Description	Example quotes
Parents' decision about consulting their GP	Parents describing their decision to consult a health professional.	<i>"It was honestly because nursery [...] And they said, you know, "We think you should go and see a GP." And they deal with lots of children every day and have seen more sick children than I have, so I kind of trusted their judgement. "</i> (Participant #19)
		<i>"So we went to the GP just to have a look and let us know what's going on. Obviously I wasn't expecting antibiotics or anything I just went to see him to double check and she was ... I think the GP told us to get paracetamol and wait it out and she was eventually better."</i> (Participant #14)
		<i>"No. We didn't feel like we needed to [go see GP]. We've called 111 a couple of times about other things in the past and I think we feel like we probably don't need to see a GP unless it's something that we feel is actually very unusual or very severe. I think at this stage now that she is two, I think we are familiar with what is severe and what a run of the mill infection is."</i> (Participant #20)
		<i>"I was happy, I think when it comes to the care of a child I'm like I want the best, most effective remedy as quickly as possible for my child to get back to a normal health level. So, I was pleased, relieved, and thankful, and I'm very thankful for the local surgery who I am very positive about."</i> (Participant #6)
Perceptions of GP management and access to healthcare	Parents' describing their experience of consulting a health professional.	<i>"I felt like it was thorough and we kind of had specific questions and that's what he focused in on and that was, yeah, it was helpful. We kind of wanted, we went there for reassurance and that's what we got basically and then, like I said, some pointers that if this, this or this happened or if he gets worse, you know, come back or ... if we were worried."</i> (Participant #11)
		<i>"...he said that [son's name] probably did have some kind of tonsillitis and because he'd been sick for a few weeks, he was in two minds about prescribing antibiotics or not, because he seemed well. [...] So, he said if he got worse and was looking like he was getting sick, then antibiotics would be the best bet, and he'd just prescribe it himself, then he wouldn't. So he wrote the prescription and I said if he gets worse I will go and cash this prescription in, and if he doesn't get worse and he's fine in himself then I would... he'll just get better naturally."</i> (Participant #8)
		<i>"And by the way the local surgery are great, however they are quite ... you know, they deal with kids readily and will put them up the waiting list, so very responsive."</i> (Participant #6)

		<i>"It must have been after he started pre-school [...] when he was coughing for about three weeks but then I couldn't get an appointment with my GP for one and a half weeks probably so I just waited until he was free because it wasn't that bad. "</i> <i>(Participant #12)</i>
Perceived appropriateness of antibiotics at GP	Parents' perceptions of the appropriateness of antibiotics.	<i>"They weren't just dishing out antibiotics for no good reason. So if that's what they recommended, then, you know, I just have Dr Google as my training, so I trusted their [GPs] judgement. "</i> <i>(Participant #19)</i>
		<i>"So I had mastitis early on breastfeeding Eliot and I was prescribed antibiotics and thank goodness I was because I was in absolute agony and I was better within 24 hours after taking them. So, again, I knew it was the right thing to do at the time because I'd read about mastitis and things and I knew that antibiotics was what I would be prescribed, so I went in knowing I would come home with them. "</i> <i>(Participant #4)</i>
		<i>"I think, in some ways, it was relief because I knew I had an option if he got sicker. It also I think when you don't want to bother doctors, so if there's a treatment at the end of the consultation it makes you feel like it wasn't for nothing, which is a probably a bit silly to evaluate [...] and I don't know, like our GPs are pretty good, I think, and so I feel like if they'd had said, well actually, he has got it but it's probably viral... I'm trying to think actually. No, I think if he'd said it's probably viral and just see how it goes, and they hadn't given me the prescription, I'd have probably been a bit more concerned because I'd be thinking, oh, I'd be watching and seeing, is it getting worse, if it gets worse I'm going to have to make another appointment. So I think it was a good decision."</i> <i>(Participant #8)</i>
		Interviewer: <i>"So the fact that she wasn't prescribed an antibiotic, you were happy with that?"</i> Respondent: <i>"Yeah, yeah, I trusted that he knew what he was talking about. I hope. And he was right, it went away. They are usually right, I find, yeah. "</i> <i>(Participant #16)</i>
		<i>"If the GP said that they were going to prescribe antibiotics I may well say is there any other thing but if they said 'This is the best thing,' then we'd go along with that. We wouldn't go into a GP appointment saying 'We need antibiotics for our daughter's condition', which I know some people do and turn up saying 'I need antibiotics'. I guess we'd take the lead from the GP. "</i> <i>(Participant #20)</i>
		<i>"Part of me thinks I don't want to just chuck antibiotics down my son's neck for the</i>

		sake of it, you know, <i>I hope I did the right thing.</i> ” (Participant #4)
		“ <i>I think I would be very conscious if it seems like she was needing them multiple times during the year. I think, for whatever reason, that would feel very unusual and I don’t think I would like that very much.</i> ” (Participant #3)
		“ <i>But if I go and they say he needs antibiotics, you know, I’d like to be in a position where I can ask more about that, you know, and just maybe have a little discussion about that before I say yes, or, you know, to say no would be ... I don’t know if I could say no to a GP, that’s the thing, like, you know, they’re supposed to be the experts. I guess that’s another thing, even though I might feel it’s not the right thing, if I said no.</i> ” (Participant #4)
Perceptions of the role of antibiotics in family life	The appropriateness of antibiotics eases pressure of modern day family life where parents need to work and children attend nursery.	“ <i>I didn’t want her condition to worsen if it was needing healthcare intervention. I also know that if she’s ill she cannot sleep as well and that disrupts my own piece of mind and my wife’s, and sleep, and our attitude to life, work the next day.</i> ” (Participant #6)
		“ <i>Allowing them to be able to go places [...]. There’s a few where if they’ve had the antibiotics then they’re allowed to attend playgroup or they’re allowed to do things. So that’s definitely a bonus because you can go, right, let’s nip that in the bud.</i> ” (Participant #2)
		“ <i>See I would continue for a good week I think, probably about a week. And depending on how much work I miss, if it was becoming over a week I would then consider, because I would start to get worried about what the employer would think.</i> ” (Participant #1)
Theme 3. Uncertainty about the risks of antibiotics and their use		
Subtheme	Description	Example quotes
Perceptions of harms of antibiotics	Parents associate the potential harms of taking antibiotics with side-effects of taking any medication, changing gut bacterial flora, and the potential to be linked to chronic conditions later in life.	“ <i>Yes, I guess a bit like any drug it would come with a list of possible side effects and I know they have to put every possible side effect that’s come up in trials so it doesn’t make for a particularly nice reading.</i> ” (Participant #13)
		“ <i>I think they can give you tummy upsets as well can’t they? And they can sort of tip all of the good bacteria out of your gut and you can get thrush and things like that, so I wouldn’t want him to get lots of tummy upsets and you know get thrush and things like that.</i> ” (Participant #11)
	Parents had conflicting perceptions about the effect of antibiotics on the	“ <i>So at the time I was uncomfortable with it [...] because there were so many babies or newborns on antibiotics from the hospital [...] the research that is going on at the</i>

	immune system. Some were unsure about the harms of antibiotics, others thoughts they were safe, and some linked antibiotic resistance as a potential harm of antibiotics.	<i>moment with regards to it being linked to asthma and eczema later on in life, and interfering with gut flora and things like that. So that concerned me too.” (Participant #1)</i>
		<i>“Because she’s young still and I think that if it’s something that she can fight it off it will help her in the long run to have a better system, a better organism that fights off viruses and stuff. If I start pumping her with antibiotics she will have a weak immune system.” (Participant #14)</i>
		<i>“And certainly I feel like it’s also probably good for her overall health to get several colds [without antibiotics], it boosts her overall immunity.” (Participant#13)</i>
		<i>“I don’t think so. I know that some people have quite severe allergies to certain types of antibiotics but no I don’t, I feel it’s a fairly safe thing to give someone.” (Participant #15)</i>
		<i>“Resistance is a big one and allergic reaction like I had is another big one so it’s not without, you know, again it’s not to be taken lightly, especially with the over usages that we’re getting now, we’d only use them in ... if it was absolutely needed.” (Participant #10)</i>
Perceptions and experiences of benefits of antibiotics	Children recover quickly on antibiotics, prevent infections from becoming more severe and support the immune system.	<i>“...he bounced within, like, the next few days. So that’s [son]’s story of antibiotics really.” (Participant #4)</i>
		<i>“So if anyone in my family told me they’re on antibiotics I’d always be, like, well, okay, because I do see them as this thing that’s a really quick prescription, a really quick fix, but then, like I say, when you’re in the moment of someone that you really love being really unwell then if it’s going to fix them and make them feel 100 times better within a couple ... I think it was literally, like, the next day he was already 90% himself, so I was, like, antibiotics are amazing.” (Participant #4)</i>
		<i>“So yes both from a NHS cost efficiency thing if it becomes less severe and also from an individual’s health point of view if it becomes severe then I’d say it’s worth going down the antibiotic route.”(Participant #13)</i>
		<i>“Advantages, I always think it’s just a case of getting something over, getting the illness over and done with more quickly, so, kind of, helping your immune system to finish it off.” (Participant #2)</i>
Perceptions of how and when antibiotics are used	Antibiotics are used for specific infection-related symptoms; based on symptom severity and duration; and for serious infections or certain (named) illnesses.	<i>“So infections really, so if someone has, you know, a fever and pain somewhere specific, so I guess the signs of infection then you know you would need them before you got more poorly I guess to kind of squash it, if that’s the right word.” (Participant #11)</i>
		<i>“If they were in a lot of pain, if they had a very high temperature, if they were not</i>

	There is a perceived need to complete antibiotic courses or and take antibiotics as prescribed.	<i>themselves at all, you know, just lying around and not having much energy to jump around and stuff, then I would think.” (Participant #16)</i> <i>“[...] if it’s something more serious, severe [...] I don’t know, such as, I don’t know what kind of child diseases are that can be really bad. I remember he had once antibiotics in the summer, [...] he had like he was swollen here [pointing to cheeks] [...] I was a bit panicking because I heard that it could be mumps or he could be infertile.” (Participant #12)</i> <i>“Not common cough or cold but something more serious a bit like a chest infection or an ear infection.”(Participant #13)</i> <i>“...see that’s the other thing as well about taking them as they’re prescribed and missing doses, I’m someone who always says ‘Oh make sure you finish the course’ and my husband is like ‘Oh no, it’s fine the symptoms have gone’, and I said ‘Yeah, well that’s not how it works, you have to make sure it’s all gone’.” (Participant #11)</i>
Theme 4. Parents’ understanding of antibiotic resistance		
Subtheme	Description	Example quotes
Description and knowledge about antibiotic resistance	Parents’ understanding of antibiotic resistance ranged from bacteria learning to resist the effects of antibiotics; to when a person does not respond to antibiotics; to when individuals becoming resistant to antibiotics; or to little personal knowledge about antibiotic resistance. Parents sourced information about antibiotic resistance from news media and internet search engines, and less so from their healthcare provider.	<i>“If you use antibiotics too much then the infections don’t start to, well, the antibiotics stop working on those infections because the little bugs get used to it and they get a little bit stronger and then they just don’t work anymore.” (Participant #16)</i> <i>“I’m guessing it’s when the patient is not responding to the treatment or it’s not having an effect, but I haven’t really heard it before to be honest. Can’t be really much help, sorry.” (Participant #5)</i> <i>“...and we are slowly building a resistance to certain antibiotics because they are overly used and over prescribed and especially in primary care.” (Participant #1)</i> <i>“[...] I mean I don’t know about it, I don’t know what percentage of patients have not responded to antibiotics, how many deaths there have been because of that. I don’t know exactly what is causing that resistance. If I read more about it to, you know, to find out maybe I could give an opinion. You know, generally, from the little I know, yes, I think it’s potentially quite worrying.” (Participant #5)</i> <i>“...I’ve seen things, particularly on the BBC news, it seems to be fairly regularly they sort of say “And this wasn’t able to be treated by antibiotics” (Participant #11)</i> <i>“You know, I don’t ... everybody would generally say the GP, I mean in the current NHS situation I don’t think the GP can really have the time to explain this, so I wouldn’t go to the GP. I would go to Google.” (Participant #5)</i>

Antibiotic resistance associated with frequent antibiotic use and inappropriate behaviours	Antibiotic resistance occurs predominately because of antibiotic overuse, using antibiotics for inappropriate indications (e.g. viral infections) or not completing antibiotic course promotes antibiotic resistance.	<i>"...so I understood that there's a problem with an overuse of antibiotics, so the more we use them the more that the bacteria can build up a resistance against the antibiotics and that causes a massive problem" (Participant #4)</i> <i>"[...] And if antibiotics are taken for infections that aren't bacterial, it could cause the resistance, and then in future the resistance can then cause this and this" (Participant #1).</i> <i>"Not a lot again other than I assume that if something is used a lot then it loses its effectiveness." (Participant #13)</i> <i>"Basically it's a matter of if you don't take the full courses than the surviving bacteria can then mutate and are then resistant, well they are resistant at that stage, to the antibiotic you are taking ..." (Participant #10)</i> <i>"Perhaps not all of the time, because over time bacteria do mutate, so they could just be a new strain that has appeared, not necessarily because of the antibiotics." (Participant #1)</i> <i>"And the other issue is all the anti-bacterial wipes that you see for everything and you know, and that's also not good and you know, the cleaning products and all that, I mean certainly there is a time and a place for them but not as a kind of everyday thing." (Participant #10)</i>
	Some parents thought that using household antibacterial products promotes antibiotic resistance, and others thought that antibiotics were not solely to blame for antibiotic resistance.	
Theme 5. Perceived consequences of antibiotic resistance		
Subtheme	Description	Example quotes
Implications of antibiotic resistance for patients	Antibiotic resistant infections can be more severe, make recovery from infections longer, with serious consequences and put certain patient groups (chronic health problems, young, old) at risk of serious illness.	<i>"[...] I guess like the last infection I had, when I had to have two courses of antibiotics, I do wonder if that was related to being resistant against the first lot of antibiotics and I don't know how many different types of antibiotics there are but, and I don't know if the first lot I was prescribed didn't work because I was resistant so they had to try a different one. I think I did ask the doctor about that as well, actually, because I was, I did wonder why the first lot didn't work. So perhaps I was resistant to them." (Participant #16)</i> <i>"And this will eventually cause problems if it continues, people won't be able to treat simple infections, people will start dying" (Participant #1)</i> <i>"[...] catching infections that could become much more severe than they would have previously. The body's natural immunity might not be as effective as it would normally be." (Participant #1)</i> <i>"I suppose vulnerable patients may well die from bugs or diseases which affect them."</i>

		<i>Patients who are elderly, patients who have multiple health problems, and I suppose the young as well, babies and infants, people who are vulnerable would probably suffer because they would be more at risk from diseases and bugs.” (Participant #20)</i>
Impact of antibiotic resistance on close family	Some parents perceived their own family at low risk of antibiotic resistance or unlikely to affect current generation. Some parents thought that antibiotic resistance would likely affect everyone the same whilst other parents perceived that antibiotic resistance would likely affect younger children more than the parents. Other parents were uncertain about the implications.	<i>“I would say we are relatively low risk. I’m kind of, of the school of let kids eat a bit of mud and don’t blast everything with Dettol. I believe ... I think it’s important that you have your own little healthy microbiome that helps your immune system function as well as it ca.” (Participant #19)</i>
		<i>“I’m not sure whether it will. As far as I understand, and I don’t understand much, it’s looking ahead so perhaps my daughter’s generation or the generation afterwards, just thinking long term, that at some point there might be a bigger health crisis if there was a bug that couldn’t be treated with antibiotics and there wasn’t anything new to treat it with, it could be something big like ... just big health problems do happen. If you look into history, routinely something big will come up whether it’s Spanish flu or whether it’s something else. These things can sort of explode.” (Participant #20)</i>
		<i>“I don’t think so. Not as far as I’m aware, no. I don’t think so. I know that there could be more health problems and different social demographics and that there is perhaps a bit of an inequality in people in a lower social demographic. They might have a shorter life expectancy or something like that. In terms of antibiotics, I wouldn’t have thought it would make a difference as far as I know.” (Participant #20)</i>
		<i>“I think because he’s younger, I mean he’s much younger, if he got an infection that antibiotic resistance would be a lot more serious for him than if I got it, I mean potentially life threatening, you know, for a two-year-old to get some kind of multi [dose] resistance nastiness.” (Participant #7)</i>
		<i>“Because it’s not real at the moment, you know, it’s not affected me [...] I haven’t seen it affect anyone that I know, and I think those sorts of things are still very abstract.” (Participant #3)</i>
		<i>“So obviously when people are really, really ill there’s nothing around to help because these super bacteria, or whatever, have become more and more resistant, so it’s going to be a massive problem in the future.” (Participant #4)</i>
Healthcare implications	Resistant bacteria present a wider health problem: impact on healthcare services; need further interventions to treat infection; make	<i>“I suppose what I mean is, although I wouldn’t pretend I know what I’m talking about, but if there were conditions and diseases that we currently treat routinely which at some point we can’t treat or that the bugs become resistant so that new strains of them present a new health ... sort of a wider health problem, just because</i>

	future courses of antibiotic ineffective; and cost the NHS more.	<i>that would seem to be a step back if we think of medicine progressing somewhere.” (Participant #20)</i> <i>“And NHS services might be struggling more in future, and then if you need to get an appointment for yourself, then you may struggle.” (Participant #1)</i> <i>“Taking a further course some years down the line would not actually treat the infection appropriately, effectively. And I may need further intervention to treat that infection.” (Participant #6)</i> <i>“[...] it could just make life more difficult for them in that if you got an infection, you can only have antibiotics that are given through a drip, or, you know, the third line or fourth line antibiotics, which means you have to be in hospital for that or, you know, and it's a lot more expensive” (Participant #7)</i>
Theme 6. Ways to reduce antibiotic resistance in response to campaign materials		
Subtheme	Description	Example quotes
Healthy lifestyle choices to reduce antibiotic resistance	Parents perceived changing one's lifestyle through healthy diet and exercise can reduce reliance on antibiotics; and using less household anti-bacterial products can reduce antibiotic resistance.	<i>“...encourage others to self-manage their healthcare, their own healthcare, and particularly through diet, appropriate consumption of liquids, and also exercise. [...] If people look after their bodies across the spectrum in various ways that that I think will reduce demand on NHS resources and carving or feeling of entitlement for medication.” (Participant #6)</i> <i>“Eat more well, eat less processed food and basically it's ... I suppose it's happening as a result of what we put in our bodies, no? About the chemicals.” (Participant #5)</i> <i>“And some of the products you use have antibiotics, or antibacterial agents in, I think less of them should be around, because obviously I think that is perhaps causing a low kind of level resistance as well.” (Participant #1)</i>
Prudent use of antibiotics	Saving antibiotics for when you really need them; using antibiotics appropriately; and completing antibiotic courses reduces antibiotic resistance.	<i>“[...] there's a point so when do you need it and when you don't and save it for more severe cases for yourself.” (Participant #12)</i> <i>“Don't take them [antibiotics] for things when you don't need them.” (Participant #16)</i> <i>“Mainly, make sure that if any of them do need antibiotics that they take all of them, that it's done as it should be done, and, yes, complete the course and just, kind of, yes, follow the instructions really.” (Participant #2)</i>
Theme 7. Parents' reflections on current antibiotic awareness materials		

Subtheme	Description	Example quotes
Perceived personal relevance of campaigns	Parents had never seen examples of public antibiotic awareness campaigns and were unaware of some of the key issues contributing to antibiotic resistance and that antibiotics are used beyond infections.	<i>“[the Antibiotic Guardian leaflet] It tells a story and it tells you what to do and what not to do, so yeah. Shame it's not in more places.”(Participant #19)</i> <i>Is that for the [antibiotic resistance] the reason actually is, from the overuse of antibiotics?” (Participant #5)</i> Interviewer: <i>“And can you think of any other areas, beyond infections, where we would use antibiotics?”</i> Respondent: <i>“No. Just to fight off infections, yeah. Why, what are the other ones?” (Participant #16)</i>
Perceptions of enablement of campaign messages	Parents were happy to avoid antibiotics, but this depended on the child's symptoms, duration and severity and their parental experience. Some parents did not appreciate scaremongering in the leaflets, and highlighted the antithesis between getting better without antibiotics, and people dying without them.	<i>“Generally, so a cough and a cold, I'd be happy with. Temperature that's responding to Calpol I'm happy with, general lethargy isn't a bad thing all the time. So yes, that sort of thing, so just kind of low level and even things like rashes and again having had a few children they've all had different things. So my youngest had slap cheek now and I think he's probably had it. I've been through it so I know what it is. The rash didn't worry me or alarm me, the temperature didn't worry me or alarm me.</i> <i>[...] I think earache is one of those, I don't know why but I think I would almost always take them to the doctor straightaway. I think partly because it's really uncomfortable and I know how uncomfortable it is. But again, I think if it was one of those and I don't know if he has had earache a couple of times but when they're pulling at their ear when they're generally unwell but again I think if it responds to Calpol or some kind of pain relief and it's not getting progressively worse I think I probably wouldn't go straightaway.”(Participant #15).</i> <i>“What do I think about the message? I think it's okay. I think because it's a poster, I suppose it's saying that you can get well soon, you can get well on your own without taking antibiotics. I think, I suppose the problem is that there's a mixed message and there's like some nuance in the middle, so when it comes to like Public Health messaging you've got, on the one hand you're saying that actually the vast majority of infections, you can get well without antibiotics, you don't need them, you can just get well on your own. And then, on the other hand, they're saying that in the world in the future where we don't have antibiotics, people might die. So, like how do you balance it? On the one hand, you've got a fear message, and, on the other hand, you've got a positive message. So, this is focusing on the positive message of you can get well soon without antibiotics, but both of those messages fight against each other.</i>

		<i>So, because if people think, oh, you can get well without antibiotics, why should I be worried about a world without antibiotics.” (Participant #8)</i> <i>“I would say, first of all, don’t resort to scaremongering, even though it’s good to know the facts I’m not saying that the facts are wrong, of course, but maybe present it in a less daunting way, and definitely connect it to what we can do and don’t just give a website. I’ve never seen this before, I’m actually laughing because I’ve never seen raising someone’s fear and then, oh, here’s a website.” (Participant #5)</i>
Theme 8. Social responsibility to inform parents about antibiotic resistance		
Subtheme	Description	Example quotes
Better communication about antibiotics and antibiotic resistance, and diagnostic tools during clinical consultations	Parents were aware that there is a drive for GPs to reduce antibiotic prescribing but wanted more transparent communication from GPs with a clear plan and explain the reasons why antibiotics were prescribed. Parents also wanted GPs to have better tools to distinguish infections that needed antibiotics.	<i>“[...] they are trying to cut down on the number of antibiotics prescribed in surgeries.” (Participant #1)</i>
		<i>“...it’s all about the communication and the feeling of control and feeling that you can go back. So, I think a lot of parents, you worry about this, if you went to the doctor and they were like... and your child is clearly unwell, and like listless or not themselves, high fever, and they don’t do anything, then you’d be like what’s going on. And you kind of need to know where the cut-off is and where you’re like at this point your child will, you know, at this point we’ll see him in hospital or at this point like...” (Participant #8)</i>
		<i>“... it would give me more confidence to have a discussion with a GP around knowing the facts about why they were being prescribed.” (Participant #4)</i>
		<i>“Do you remember the machine that could decide whether it was viral or bacterial? [...] and then they would say, oh, antibiotics is definitely needed here or no. So, I thought that was amazing and that every GP practice should have one tomorrow, but then if it’s not that accurate then maybe it’s not the answer. But something like that needs to happen where every practice has a tool or something that can give GPs more confidence and something they can rely on, because it’s not working at the moment and it’s getting more and more out of hand. So, yes, something needs to be invented.” (Participant #4)</i>
Provide better public campaign strategies on antibiotic resistance in terms of content, timing, and targeting populations	Parents suggested that future campaigns should target people about antibiotic stewardship in a context outside illness, using a simple universal message specific to individuals and families. Parents	<i>“I think maybe it’s the little things as much as the big things. So, for me, using drugs appropriately is a big thing, but maybe more about what you can do in everyday life, because I don’t know if there are things that you can do that I don’t do and it hasn’t occurred to me. Honestly, it’s never occurred to me to think about it properly before now in a context outside kind of illness. So that’s probably my societal duty to go and look it up”. (Participant #19)</i>

	wanted information about antibiotics and resistance through face-face encounters, dissemination that fits into their everyday lives.	<i>“Perhaps aim it more at the patient and their family, and say what implications it could have for them directly in future I think yes [...] Because you tend to read things like this and easily forget it, whereas if you realise it may have problems for your children in future for example, then you do start to worry a bit more, and it is something you remember then from having future appointments I think.” (Participant #1)</i>
		<i>“But I think it’s just catching every ... ensuring you catch every family with an under five-year-old, or every family. So, I know some of the political parties have put information through your door, so whether it’s a leaflet that is delivered right across the land” (Participant #6)</i>
		<i>“If there was something that said, antibiotics can help you get better in five days but you could get better yourself without taking them in seven days, you might go, oh okay, that might be something that we could try.” (Participant #18)</i>
		<i>“Perhaps I would find it useful to know definitively, if that can be said, what needs antibiotics and what doesn’t. I think you learn as a parent over time what kind of ill is normal ill and what’s not. Perhaps it would be useful to know what things really don’t need antibiotics and then you’ll be, I think, more confident with the fact you can give Calpol and you don’t need to go to the doctor if it’s X, Y or Z or if the symptoms are like that.” (Participant #20)</i>
		<i>“I think that being able to feel that you can get that reassurance I think it’s really important and whether that’s in the form of access to healthcare or a leaflet. We [received] so much information when you first have a baby, any baby, even the fourth. I don’t know if that’s [already] included but I think it would be useful to give that information really.” (Participant #15)</i>

APPENDIX 26 – Publication from thesis

van Hecke O, Wang K, Lee JJ, Roberts NW, Butler CC.

Implications of Antibiotic Resistance for Patients' Recovery From Common Infections in the Community: A Systematic Review and Meta-analysis.

Clin Infect Dis. 2017 Aug 1;65(3):371-382.

doi: 10.1093/cid/cix233.

Implications of Antibiotic Resistance for Patients' Recovery From Common Infections in the Community: A Systematic Review and Meta-analysis

Oliver van Hecke,¹ Kay Wang,¹ Joseph J. Lee,¹ Nia W. Roberts,² and Chris C. Butler¹

¹Nuffield Department of Primary Care Health Sciences, University of Oxford, and ²Bodleian Health Care Libraries, Knowledge Centre, Oxford, United Kingdom

Background. Antibiotic use is the main driver for carriage of antibiotic-resistant bacteria. The perception exists that failure of antibiotic treatment due to antibiotic resistance has little clinical impact in the community.

Methods. We searched MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and Web of Science from inception to 15 April 2016 without language restriction. We included studies conducted in community settings that reported patient-level data on laboratory-confirmed infections (respiratory tract, urinary tract, skin or soft tissue), antibiotic resistance, and clinical outcomes. Our primary outcome was clinical response failure. Secondary outcomes were reconsultation, further antibiotic prescriptions, symptom duration, and symptom severity. Where possible, we calculated odds ratios with 95% confidence intervals by performing meta-analysis using random effects models.

Results. We included 26 studies (5659 participants). Clinical response failure was significantly more likely in participants with antibiotic-resistant *Escherichia coli* urinary tract infections (odds ratio [OR] = 4.19; 95% confidence interval [CI] = 3.27–5.37; n = 2432 participants), *Streptococcus pneumoniae* otitis media (OR = 2.51; 95% CI = 1.29–4.88; n = 921 participants), and *S. pneumoniae* community-acquired pneumonia (OR = 2.15; 95% CI = 1.32–3.51; n = 916 participants). Clinical heterogeneity precluded primary outcome meta-analysis for *Staphylococcus aureus* skin or soft-tissue infections.

Conclusions. Antibiotic resistance significantly impacts on patients' illness burden in the community. Patients with laboratory-confirmed antibiotic-resistant urinary and respiratory-tract infections are more likely to experience delays in clinical recovery after treatment with antibiotics. A better grasp of the risk of antibiotic resistance on outcomes that matter to patients should inform more meaningful discussions between healthcare professionals and patients about antibiotic treatment for common infections.

Keywords. antibiotic resistance; primary care; clinical significance.

Antibiotic resistance is recognized as an important societal health issue. Yet members of the public consider the risk of antibiotic resistance to apply to society at large and in the distant future, rather than constituting a risk to their own health, and primary-care clinicians report that they rarely encounter treatment failure because of antibiotic resistance, leading to the perception that antibiotic resistance is remote from prescribing decisions [1–3]. This major evidence gap may influence expectations for antibiotics and antibiotic-prescribing decisions in the community [4, 5].

Although the consequences of antibiotic-resistant infections in hospitalized patients are known (increased mortality, longer

hospital stays, and increased healthcare costs) [6, 7], antibiotic resistance may also have important consequences for patients with common infections managed in the community [8]. Approximately 300 million primary-care consultations in the United Kingdom and 490 million consultations in the United States each year [14, 17] are for respiratory-tract (10%–20%) [9–11], urinary-tract (1%–3%) [12, 13], and skin and soft-tissue infections (1%) [14–16]. Almost 75% of all antibiotics in the United Kingdom are prescribed in primary care [18] and at considerable cost [19–21].

Antibiotic use is also the most important risk factor for carriage of antibiotic-resistant bacteria [22, 23] and the development of subsequent antibiotic-resistant infections. However, the clinical relevance of antibiotic resistance for patients with common infections in the community is less well understood. This systematic review aims to compare clinical outcomes between antibiotic-resistant and antibiotic-sensitive infections in the community for patients with respiratory-tract, urinary-tract, and skin or soft-tissue infections.

Received 22 November 2016; editorial decision 22 February 2017; accepted 14 March 2017; published online March 20, 2017.

Correspondence: O. van Hecke, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Rd, Oxford OX2 6GG, UK (oliver.vanhecke@phc.ox.ac.uk).

Clinical Infectious Diseases® 2017;65(3):371–82

© The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/cid/cix233

METHODS

Search Strategy and Inclusion Criteria

We systematically searched electronic databases (MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and Web of Science) from inception to 15 April 2016 with no language restrictions. We used the Medical Subject Headings (MeSH) terms and validated search filters for “antibiotic resistance” [23] and “primary care/community setting” [24] and keywords “antibiotic resistance,” “skin or soft tissue infections,” “respiratory tract infections,” “otitis media,” and “urinary tract infections” (Supplementary Data Files 1 and 2). The review protocol was registered on the PROSPERO database (CRD42015032441).

Observational studies and randomized controlled trials (RCTs) were eligible for inclusion if the study was conducted in a community setting (general practice, hospital outpatient clinic, or emergency department) and reported patient-level data on laboratory-confirmed potentially pathogenic infections, antibiotic resistance, and clinical outcomes. Studies solely conducted in hospital inpatient settings, involving patients with hospital-acquired infections and highly specific patient groups in whom specialised antibiotic treatment strategies are recommended (eg, cystic fibrosis), were excluded.

We categorized respiratory-tract infections (RTIs) into community-acquired pneumonia (CAP), sore throat/pharyngitis, acute otitis media (AOM), and acute maxillary sinusitis (AMS).

Our primary outcome was clinical response failure, which we defined as the persistence of symptoms after completion of antibiotic treatment. Where studies reported outcomes at >1 time point, we selected the time point closest to 7–14 days from baseline to reflect the duration of typical antibiotic regimens. Secondary outcomes were reconsultation, further antibiotic prescriptions (both within 30 days from baseline), symptom duration, and symptom severity.

Data Extraction and Risk of Bias Assessment

Two reviewers (O. V. H., J. J. L.) independently extracted data on the characteristics of included studies (Table 1 and Supplementary Data File 2). For RCTs, outcome data for antibiotic-resistant and antibiotic-sensitive infections were extracted separately for each treatment arm because RCT studies only determined whether infections were antibiotic-resistant or antibiotic-sensitive after patients had already been randomized, hence randomization was not stratified according to antibiotic resistance.

Data had to be reported in sufficient detail to assess relevant outcomes between patients with antibiotic-resistant and antibiotic-sensitive infections in order to construct a 2×2 contingency table. Where possible, we extracted outcomes for antibiotic-resistant and antibiotic-sensitive infections whereby resistance and sensitivity were defined in relation to the same antibiotic or class of antibiotic as the antibiotic being prescribed.

If studies reported intermediate levels of antibiotic resistance for certain infections, these were classified as antibiotic-resistant infections in our analysis. If there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed, studies were still included but specifically highlighted.

The quality of the included studies was assessed independently by 2 reviewers (O. V. H., J. J. L.) for RCTs and observational studies based on their respective risk-of-bias tool, namely the Cochrane Collaboration's tool for assessing risk of bias in randomized trials and critical appraisal skills programme (CASP) checklist for cohort studies (Supplementary Data File 3) [25, 26].

Statistical Analysis

To compare the odds of clinical response failure between antibiotic-resistant and antibiotic-sensitive infections, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) for infections where data were available from ≥ 3 studies for the same bacterial pathogen using random effects meta-analysis. Heterogeneity was assessed using the χ^2 test and I^2 statistic. Odds ratios in relation to reconsultation and further antibiotic prescriptions were calculated using similar methods. For continuous data, we planned to plot survival curves where possible for duration and severity of symptoms in antibiotic-resistant versus antibiotic-sensitive infections.

Subgroup analyses were performed according to study design (observational studies vs RCTs) and type of healthcare setting (general practice, hospital outpatient clinic, or emergency department). Results were summarized narratively where data were not sufficient to perform meta-analysis or plot survival curves. Analysis was conducted using StataSE version 13.

RESULTS

We identified 10 681 records, of which 136 full-text articles were assessed. The most common reason for exclusion ($n = 31/110$) was that clinical outcomes were not reported separately for antibiotic-resistant versus antibiotic-sensitive infections.

Twenty-six studies were included (Figure 1), of which 13 were observational studies, 8 were RCTs, and 5 were secondary analyses of pooled RCT data [27–31]. Six studies were conducted in primary care/general practice, 12 in hospital outpatients, 1 in a mixed outpatient/primary care setting, 2 in a mixed outpatient/inpatient setting, 1 in an emergency department setting, and 4 in another community setting which was not clearly defined (Table 1). Our included RCTs and secondary analyses of pooled RCTs did not report any duplicate data.

Data relating to ≥ 1 study outcomes were available for 15 580 patients, of whom 6617 patients had a laboratory-confirmed potentially pathogenic bacterial infection. Data on whether the infection was antibiotic-resistant or antibiotic-sensitive were

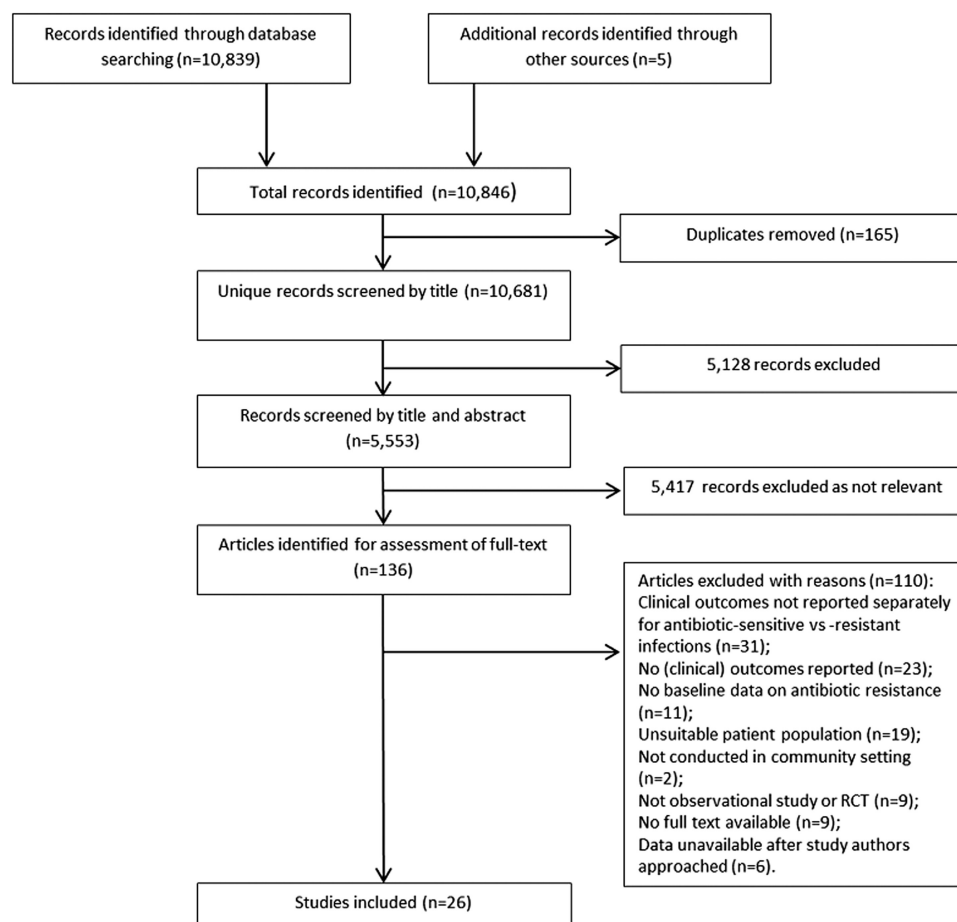


Figure 1. Study selection. Abbreviation: RCT, randomized controlled trial.

also available for 5659 of these patients (antibiotic-resistant: $n = 1268$; antibiotic-sensitive: $n = 4391$) (Table 2).

Clinical criteria for obtaining urine samples and diagnosing urinary-tract infections (UTIs) varied between studies. Diagnostic thresholds used to define *Escherichia coli* UTIs were reported as being $>10^4$ colony-forming units (CFU) in 3 studies (Supplementary Data File 4A) [32–34]. Four studies obtained urine samples from patients with urinary symptoms and positive urine dipstick test [32, 33, 35, 36], 2 studies obtained urine samples from patients with urinary symptoms only [37, 38], 1 study obtained urine samples from patients with “clinically suspected” UTI [8], and 2 studies did not report selection criteria for obtaining urine samples [34, 39]. Most UTI studies counted infections of mixed uropathogens as indicating an infection; however, the dominant bacterium ($>65\%$) was *E. coli* in all UTI studies. Where calculations were possible, the proportion of clinically suspected UTIs that had a laboratory-confirmed infection was 57%–95%. Three studies based clinical diagnosis of *S. pneumoniae* CAP on symptoms, radiographic evidence, and blood tests [29, 40, 41], 1 study based diagnosis on symptoms and blood tests [30], and 1 study [31] did not report how

a diagnosis was established (Supplementary Data File 4B). Diagnostic criteria for *S. pneumoniae* AOM (Supplementary Data File 4C) were more uniform (symptoms, examination, and tympanocentesis) except for 1 study for which this was not reported [31].

Data relating to our primary outcome (clinical response failure) were available from 13 RCTs [27–31, 37, 38, 40, 42–46] and 9 observational studies [8, 32–34, 36, 39, 41, 47, 48]. Three observational studies reported data on reconsultations [8, 32, 35]; 4 studies reported data on further antibiotic prescriptions [8, 34, 49, 50]; 4 studies reported data on symptom duration [8, 32, 49, 50]; and 1 study reported data on symptom severity [50]. Data on these outcomes were not reported by any RCTs or secondary analyses of pooled RCT data.

The appendix (Supplementary Data File 3) summarizes our risk of bias assessment of included studies. For 12 of 13 RCTs, there was low risk of reporting bias [27–29, 31, 37, 38, 40, 42–46]. Only 1 RCT reported assessing outcomes blinded from knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive [42]. We were not able to assess whether RCTs considered confounding variables between

Table 1. Characteristics of 26 Included Studies (Primary and/or Secondary Outcomes) According to Infection

Study	Country	Setting	Infection type	Study design	Participants	Potential pathogen being studied	No. of potential pathogens being studied with evidence of antibiotic resistance				Primary outcome time point ^{a,b}	Secondary outcomes ^c	Treatment antibiotic/ antibiotic class ^d	Antibiotic to which resistance measured	
							Total no. recruited	Total no. with potential pathogen being studied	No. of patients where resistance and outcome data available	No. of patients where resistance and outcome data available					
Urinary-tract infection															
Brown et al (2002) [35]	United States	OP/ PHC	UTI	Obs (R)	Women	E	NR	601 isolates ^e	44	104	...	Rec ^c	TMP-SMX	TMP-SMX	
Butler et al (2006) [8]	United Kingdom	PHC	UTI	CC Obs (P)	Adults	E	932	922	94	797 [1] 862 (Rec) [2] 816 (Fab) [2] 420 (Sdur) [2]	Within 30 days	Rec ^c Fab ^c Sdur ^c	Not specified	To prescribed antibiotic [1] To at least 1 antibiotic [2]	
Gupta et al (2007) [37]	United States	PHC	UTI	RCT	Women	E	338	276	34	308 ^f	Day 3 ^b	...	TMP-SMX	Nitrofurantoin	TMP-SMX
Little et al (2010) [50]	United Kingdom	PHC	UTI	Obs (P)	Women	NR ^g	843	NR	NR	264 (Sdur) 264 (Ssev)	-	Sdur ^c Ssev ^c	Not specified	To >1 antibiotics	
McNulty et al (2006) [32]	United Kingdom	PHC	UTI	Obs (P)	Women	E	497	298 ^h	44	207 (Sdur) ^f 317 (Rec)	Day 7 ^b	Sdur ^c Rec ^c	Trimethoprim	Trimethoprim	
Noskin et al (2001) [33]	United States	OP	UTI	Obs (P)	Women	E	156	89	42	71	NR ^b	...	Not specified	To >1 antibiotics	
Raz et al (2002) [36]	Israel	OP	UTI	Obs (P)	Women	E	618	425	30	484 ^f	Days 5–9 ^b	...	TMP-SMX	TMP-SMX	
Soraas et al (2014) [34]	Norway	Other	UTI	Obs (P)	Adults	ESBLE	343	343 ⁱ	81 (ESBLE)	343	Within 14 days ^b	Fab ^c	Mecillinam Nonmecillinam	Mecillinam and ESBL status	
Vallano et al (2006) [39]	Spain	PHC	UTI	Obs (P)	Women	E	220	88	15 ^f	108 ^f	Within 14 days ^b	...	Not specified	To >1 antibiotics	
Van Merode et al (2005) [38]	Netherlands	PHC	UTI	RCT	Women	E	324	80	17	114 ^f	Days 6–8 ^b	...	Trimethoprim	Trimethoprim	
Community-acquired pneumonia															
Cao et al (2010) [49]	China	OP	RTI (CAP)	Obs (P)	Adults; adolescents	MP	356	67	46	59	...	Fab ^c Sdur ^c	Not specified	Erythromycin	
Hagberg et al (2003) [29]	Multiple	IP/OP	RTI (CAP)	Pooled data from 6 phase III trials	Adults	SP	1373	174	23 ^j	174	Days 3–5 ^b	...	Telithromycin	Penicillin or erythromycin	
Kawai et al (2012) [51]	Japan	OP	RTI (CAP)	Obs (P)	Children; adolescents	MP	476	50	21	30	...	Fab ^c	Not specified	To >1 macrolide	
O'Doherty et al (1997) [40]	United Kingdom; Ireland	OP	RTI (CAP)	RCT	Adults	SP	264	30 ^k	6	30	Days 3–5 ^b	...	Grepafloxacin Amoxicillin	Amoxicillin	
Van Rensburg et al (2005) [30]	Multiple	OP	RTI (CAP)	Pooled RCT (8 phase III trials and 1 phase II study)	Adults	SP	2339	418	61	327	Days 17–24 ^b	...	Telithromycin	To erythromycin and penicillin	
Yanagihara et al (2004) [41]	Japan	OP	RTI (CAP)	Obs (R)	Adults	SP	306	306	129	306	NR ^b	...	Not specified	Penicillin	
Zhan et al (2014) [31]	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adults; children	SP	872/ 309 CAP	CAP 79	CAP 27	CAP 79	NR ^b	...	Azithromycin	Azithromycin	

Study	Country	Setting	Infection type	Study design	Participants	Potential pathogen being studied	Total no. recruited	Total no. with potential pathogen being studied	No. of potential pathogens being studied with evidence of antibiotic resistance	No. of patients where resistance and outcome data available	Primary outcome time point ^{a,b}	Secondary outcomes ^c	Treatment antibiotic/ antibiotic class ^d	Antibiotic to which resistance measured
Acute otitis media														
Barry et al (1994) [27]	France	OP	RTI (AOM)	Pooled data from 3 RCTs	Children	SP	1092	236	54 ^m	219	Day 10	...	B-lactams (combined)	Penicillin; B-lactams
Dagan et al (1996) [42]	Israel	ER	RTI (AOM)	RCT	Children	SP	266	98	18	77	Day 10	...	Cefuroxime Cefaclor	Cefuroxime Cefaclor
Hoberman et al (1996) [47]	Multiple	IPOP	RTI (AOM)	Obs (P)	Children	SP	917	298	82	260	Days 12–14 ^b	...	Co-amoxiclav	Penicillin
Hoberman et al (2005) [45]	Multiple	OP	RTI (AOM)	RCT	Children	SP	730	229	158	188	Days 12–14 ^b	...	Co-amoxiclav Azithromycin	Penicillin Azithromycin
Zhan et al (2014) [31]	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adults; children	SP	872 ^l AOM 402	AOM 177	AOM 41	AOM 177	NR	...	Azithromycin	Azithromycin
Acute sore throat														
Quinn et al (2003) [46]	United States; Canada	OP	RTI (sore throat)	RCT	Adults; adolescents	Spy	526	360 ⁿ	9	285	Days 16–23 ^b	...	Telithromycin Clarithromycin	Erythromycin
Seppälä et al (2002) [48]	Finland	OP	RTI (sore throat)	Obs (R)	NR	Spy	NR	529	76	273	NR	...	Erythromycin Penicillin	Erythromycin
Acute maxillary sinusitis														
Buchanan et al (2005) [28]	Sweden	Other	RTI (AMS)	Pooled data from 3 RCTs	Adults; adolescents	SP	1298	126	1	78	Days 17–24 ^b	...	Telithromycin	Telithromycin
Zhan et al (2014) [31]	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adults; children	SP	872 ^l AMS 161	AMS 57	AMS 19	AMS 57	NR	...	Azithromycin	Azithromycin
Skin and soft-tissue infection														
Dagan et al (1992) [43]	Israel	OP	Skin (Imp)	RCT	Children	SA	102	90	27	89	Days 3–8	...	Erythromycin Mupirocin	Erythromycin Mupirocin
Gordano et al (2006) [44]	United States	Other	Skin (USSSI)	RCT	Adults; adolescents	SA	392	171	79	151	Days 17–24 ^b	...	Cefdinir Cephalixin	Methicillin
Overall							15580			5659 [3]				

Abbreviations: AMS, acute maxillary sinusitis; AOM, acute otitis media; CAP, community-acquired pneumonia; CC, case control; E, *Escherichia coli*; ER, Emergency room; ESLE, extended spectrum β -lactamase *Escherichia coli*; Imp, impetigo; IP, hospital inpatient; MP, *Mycoplasma pneumoniae*; NR, not reported; Obs (P), prospective observational; Obs (R), retrospective observational; OP, hospital outpatient; Other, community setting (not specified); PHC, primary care clinic/general practice; RCT, randomized controlled trial; RTI, respiratory-tract infection; SA, *Staphylococcus aureus*; SP, *Streptococcus pneumoniae*; Spy, *Streptococcus pyogenes*; TMP-SMX, trimethoprim-sulfamethoxazole; USSSI, uncomplicated skin and skin structure infections (eg, cellulitis, erysipelas, impetigo, simple abscess, wound infection, furunculosis, folliculitis); UTI, urinary-tract infection.

^aPrimary outcome: “response failure” defined as the persistence of symptoms after completion of antibiotic treatment. Where the outcome was reported as “clinical cure” in the study, we calculated the proportion of patients that had failed to respond to antibiotic treatment within the designated timescale (ie, 1 – proportion of patients with clinical cure).

^bData on clinical cure, rather than clinical response failure, were reported by 10 randomized controlled trials [28–31, 37, 38, 40, 44–46] and 7 observational studies [32–34, 36, 39, 41, 47]. Overall, clinical response failure was assessed 3–5 days from baseline in 3 studies [29, 37, 40], 6–10 days from baseline in 6 studies [27, 32, 36, 38, 42, 43], 11–14 days from baseline in 4 studies [34, 39, 45, 47], 20–30 days from baseline in 5 studies [8, 28, 30, 44, 46], and not reported in 4 studies [31, 33, 41, 48].

^cSecondary outcomes: reconsultation (Reo), further antibiotic prescriptions (Fab), symptom duration (Sdur), and symptom severity (Ssev).

^dMultiple antibiotics prescribed in separate study arms.

^eWe assumed 1 isolate per participant.

Table 1. Continued

¹ All combined pathogens.
² Specific organism not reported.
³ Coliforms; 242 single isolates were sent to HPA Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) of which <i>Escherichia coli</i> accounted for 90% (n = 219/242).
⁴ ESBL <i>E. coli</i> and non-ESBL <i>E. coli</i> only.
⁵ Penicillin- or erythromycin-resistant (all <i>Streptococcus pneumoniae</i> isolates were susceptible to telithromycin).
⁶ Only 81 were evaluated microbiologically.
⁷ Excluded acute exacerbations of chronic bronchitis.
⁸ One child in the SpRP group did not complete the treatment course because of adverse events and was not evaluable for clinical response.
⁹ Positive screening for group A β -haemolytic streptococcus.
...not applicable [1].: Resistance measured to prescribed antibiotic [2].: Resistance measured to at least one antibiotic [3].: where more than one outcome data available, the lowest number was taken.

antibiotic-resistant and antibiotic-sensitive infections except for 1 RCT [42] because baseline characteristics of the study population were not reported according to whether participants had an antibiotic-resistant or antibiotic-sensitive infection.

For the 13 observational studies, participants were representative of the defined population except for 1 study [34] and generally clearly defined. Antibiotic exposure was accurately measured (eg, secure medical records) in 10 studies [8, 32–34, 36, 39, 41, 48–50]. Only 6 observational studies attempted to address potential confounders, and measurement of outcome was only satisfactorily blinded in 2 studies [8, 35].

Figures 2–4 summarize odds ratios with 95% confidence intervals for participants with antibiotic-resistant *E. coli* UTIs (Figure 2), *S. pneumoniae* CAP (Figure 3), and *S. pneumoniae* AOM (Figure 4) in relation to clinical response failure. Clinical response failure was significantly more likely in antibiotic-resistant than antibiotic-sensitive *E. coli* UTIs (OR = 4.19; 95% CI = 3.27–5.37; $P < .001$; n = 2432 participants, 8 studies) [8, 32–34, 36–39]. Antibiotic-resistant *S. pneumoniae* CAP and AOM were also associated with significantly greater odds of clinical response failure (CAP: OR = 2.15, 95% CI = 1.32–3.51, $P < .002$, n = 916 participants, 5 studies [29–31, 40, 41]; AOM: OR = 2.51, 95% CI = 1.29–4.88, $P < .007$, n = 921 participants, 5 studies [27, 31, 42, 45, 47]).

Clinical heterogeneity precluded meta-analysis for skin or soft-tissue infections because data were only available from 2 studies [43, 44], of which 1 involved children with impetigo and the other involved adults and adolescents with a range of different infections, including cellulitis, simple abscesses, and wound infections (Supplementary Data File 5). Likewise for sore throat, there was uncertainty regarding similarity of study population characteristics between the 2 studies [46, 48], and for sinus infections [28, 31], 1 study [28] had only 1 patient with an antibiotic-resistant infection.

Reconsultation was significantly more likely in patients with antibiotic-resistant *E. coli* UTIs (Supplementary Data File 6A) (OR = 5.07; 95% CI = 2.17–11.82; n = 1283 participants, 3 studies) [8, 32, 35]. Data on patient reconsultations were not available for other infections. Two studies involving patients with *M. pneumoniae* CAP reported data on further antibiotic prescriptions (Supplementary File 6B) [49, 51]. However, meta-analysis was not performed because 1 study did not report which antibiotic was used to treat participants [49], and there were no outcome events among patients with antibiotic-sensitive infections in the other study [51]. Two studies involving patients with *E. coli* UTIs also reported data on further antibiotic prescriptions [8, 34]. However, treatment antibiotic was not reported in 1 study [8], and the other study focused specifically on extended-spectrum beta-lactamases (ESBL) *E. coli* infections [34].

Antibiotic-resistant infections were associated with longer duration of symptoms in 2 [32, 50] of 3 *E. coli* UTI studies

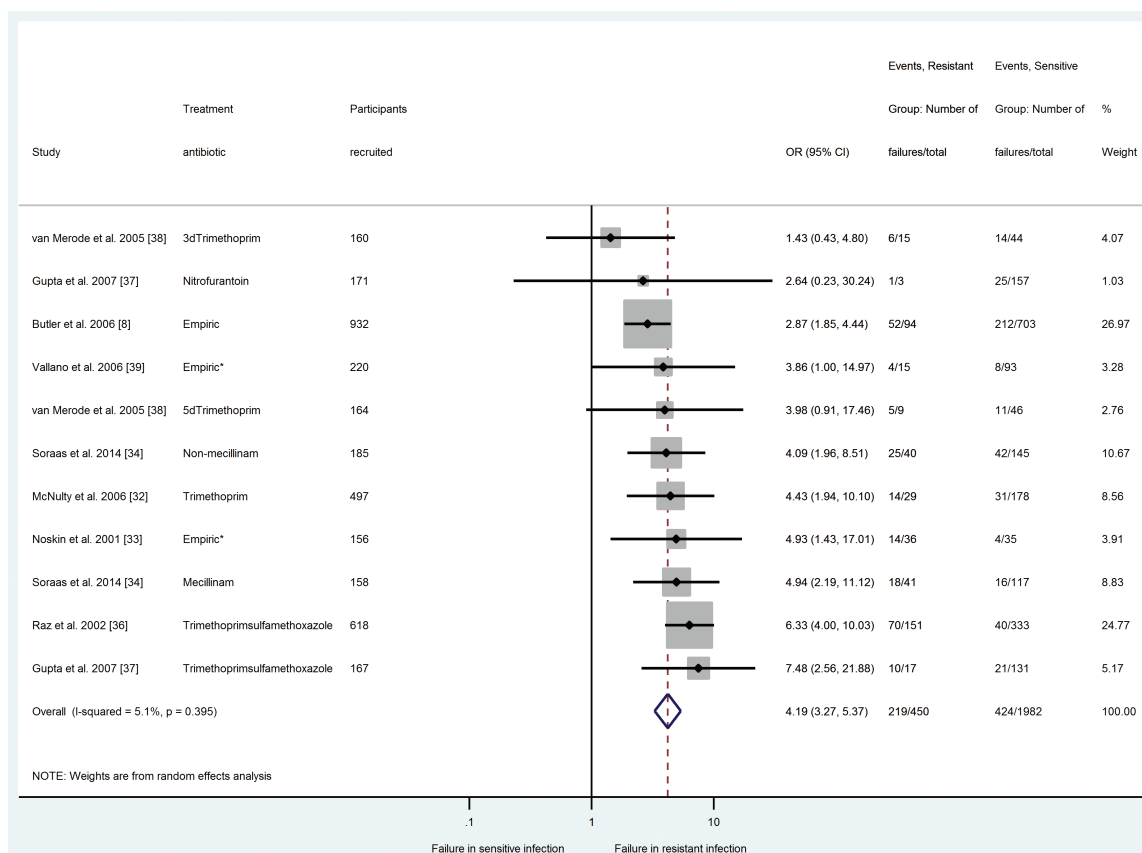


Figure 2. Comparison between antibiotic-resistant and antibiotic-sensitive (*Escherichia coli*) urinary tract infections in relation to response failure. Odds ratio > 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection. *indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed. Abbreviations: 3d, 3-day regimen; 5d, 5-day regimen; CI, confidence interval; OR, odds ratio.

(Supplementary Data File 7) [8, 32, 50], but not in the 1 *M. pneumoniae* CAP study [49]. Only 1 study compared symptom severity between antibiotic-resistant and antibiotic-sensitive *E. coli* UTIs and found that patients with resistant infections had significantly greater symptom severity between days 2 and 4 (antibiotic-resistant: 2.01, standard deviation = 0.89 vs antibiotic-sensitive: 1.47, SD = 0.88; $P < .001$; $n = 264$ participants; severity grading 0 = no symptoms, 6 = as bad as it could be) (Supplementary Data File 8) [50].

Increased odds of clinical response failure in antibiotic-resistant *E. coli* UTIs were demonstrated in both observational studies (OR = 4.28; 95% CI = 3.31–5.54) and RCTs (OR = 3.49; 95% CI = 1.53–7.97). Odds of clinical response failure were also increased among participants recruited from both hospital outpatient (OR = 5.42; 95% CI = 3.87–7.61) and primary-care settings (OR = 3.29; 95% CI = 2.38–4.56).

For *E. coli* UTIs, post hoc sensitivity analysis was conducted excluding studies conducted in areas where the prevalence of antibiotic-resistant infections was reported to be high [36], studies that examined highly specific antibiotic-resistant bacteria (eg, ESBL *E. coli*) [34], studies where the reported susceptibility did not match the treatment antibiotic class [29, 30, 40, 41], and

studies where the treatment antibiotic was not specified [33, 39]. This did not change the overall findings (OR = 3.27; 95% CI = 2.32–4.60; $n = 1426$ participants, 5 studies) [8, 32, 37, 38].

For *S. pneumoniae* CAP, the findings were no longer statistically significant (OR = 1.22; 95% CI = 0.25–5.91; $n = 91$ participants, 2 studies) [31, 40], after excluding studies where the reported susceptibility did not match the prescribed treatment antibiotic class [29, 30] or where the treatment antibiotic was not reported [41]. For *S. pneumoniae* AOM, the overall findings did not change (OR = 3.37; 95% CI = 2.04–5.56; $n = 573$ participants, 4 studies) [27, 31, 42, 45], after excluding 1 study conducted in an inpatient/outpatient setting [47].

DISCUSSION

Main Findings

Our findings demonstrate that patients who present in community healthcare settings with antibiotic-resistant UTIs and RTIs are more likely to experience clinical response failures than patients with antibiotic-sensitive infections. Patients with antibiotic-resistant *E. coli* UTIs are also more likely to consult a healthcare professional and experience prolonged and more severe symptoms than patients with antibiotic-sensitive

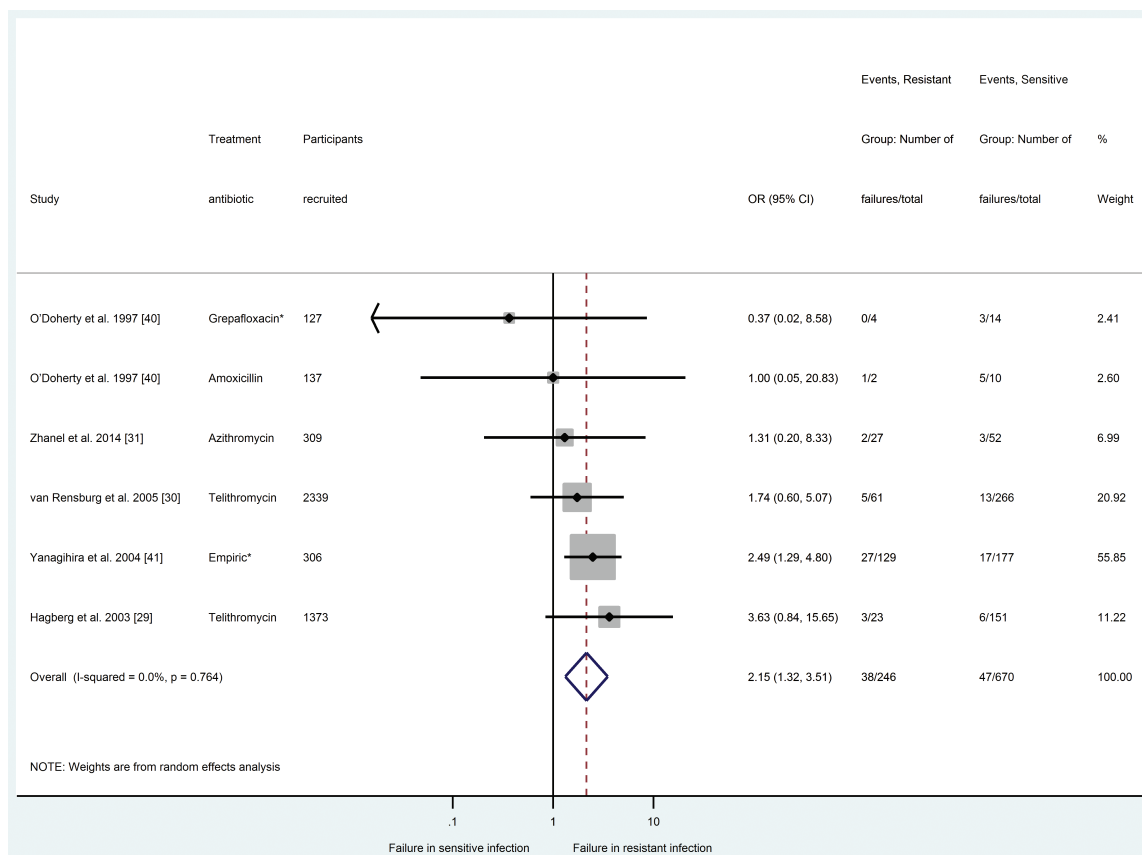


Figure 3. Comparison between antibiotic-resistant and antibiotic-sensitive (*Streptococcus pneumoniae*) community-acquired pneumonia in relation to response failure. Odds ratio > 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection. *indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed. Abbreviations: CI, confidence interval; OR, odds ratio.

infections. This challenges the perception that patients in the community are at little additional personal risk from the impact of antibiotic resistance for common infections.

Comparison With Existing Literature

Previous systematic reviews have demonstrated a clear association between commonly prescribed antibiotics in the community and carriage of antibiotic-resistant bacteria [22, 23, 52]. Our estimates are consistent with estimates of clinical response failure rates in community populations for UTIs (14%–38%) [53, 54], CAP (11%–24%) [55], and AOM (7%–24%) [56, 57]. These earlier studies did not, however, determine the specific contribution (or association) of antibiotic resistance to response failure.

We were only able to estimate reconsultation rates for *E. coli* UTIs, with our results (28%; n = 357/1283) being comparable with those of other studies (26%–55%) [58, 59].

The prevalence of resistant *E. coli* in the UTI studies we included for our primary outcome (10.4%; n = 357/3428) falls within the lower end of the spectrum compared with most community-based population estimates (5%–53%) because this depends on the antibiotic susceptibility measured, the

clinical criteria used for obtaining urine samples and diagnosing UTIs [60, S61–S63], and study population characteristics [52]. However, when examining resistance to the same antibiotic in community populations, our prevalence of *E. coli* resistant to nitrofurantoin (1.75%; n = 3/171), for example, is similar to that of other studies (<2%) [S61, S63]. Similarly, the prevalence of resistant *S. pneumoniae* in CAP and AOM in our included studies are lower than population estimates (5.4%, n = 246/4591 vs 8%–33% for CAP [S64, S65]; 0.4%, n = 353/3407 vs 1%–48% for AOM [S66, S67]).

Strengths and Limitations

Our search strategy used validated search filters, and we included both RCTs and observational studies conducted in community healthcare settings. We identified studies that may have collected but did not publish relevant data, and we contacted a sample of the authors to request unpublished and/or additional data (Supplementary Data File 2).

We focussed on more practical, clinically relevant outcomes for patients and clinicians, moving beyond a laboratory-focused, microbiological outcome. Because most of our included studies specifically excluded patients with known

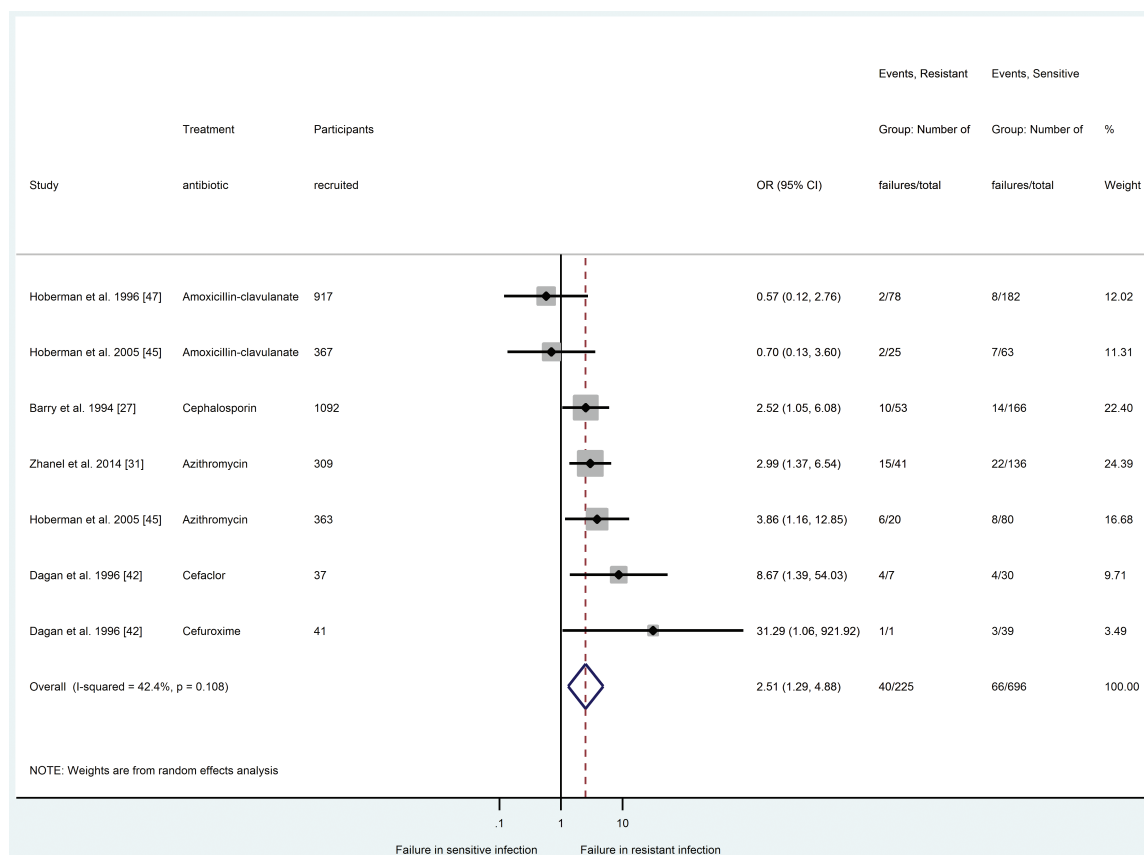


Figure 4. Comparison between antibiotic-resistant and antibiotic-sensitive (*Streptococcus pneumoniae*) acute otitis media in relation to response failure. Odds ratio > 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection. *indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed. Abbreviations: CI, confidence interval; OR, odds ratio.

medical conditions [8, 27, 28, 30, 32–40, 43–50], we may be underestimating the impact of antibiotic-resistant infections in patients with multimorbidity. Individual patient data were not available to allow us to adjust for potential confounders.

An important limitation is that antibiotic resistance is just 1 explanation for clinical response failure, which could also be due to factors such as coinfection or reinfection. We cannot say what the relative contribution of antibiotic resistance was compared with other factors that could potentially influence

the likelihood of clinical response failure. Such factors may also explain why a significant proportion of patients with sensitive infections failed to respond to antibiotics. Previous studies of failure from antibiotic treatment have been criticized because many patients probably had viral infections and would not have been expected to recover with antibiotic treatment [S68]. All included patients in our review had laboratory-confirmed bacterial infections. That said, this may limit generalizability of findings to clinical practice, given that treatment decisions in the community are based on clinical findings without

Table 2. Data Related to 1 or More Study Outcomes According to Infection Type and Bacterial Pathogen

Infection	Bacteria	No. of studies	No. of antibiotic-resistant infections	No. of antibiotic-sensitive infections
UTI [8, 32–39, 50]	<i>Escherichia coli</i>	10	523	2277
CAP [29–31, 40, 41]	<i>Streptococcus pneumoniae</i>	5	246	670
CAP [49, 51]	<i>Mycoplasma pneumoniae</i>	2	63	24
AOM [27, 31, 42, 45, 47]	<i>Streptococcus pneumoniae</i>	5	225	696
Sore throat [46, 48]	Group A β -haemolytic <i>Streptococcus</i>	2	85	473
AMS [28, 31]	<i>Streptococcus pneumoniae</i>	2	20	115
Skin infection [43, 44]	<i>Staphylococcus aureus</i>	2	106	134

Abbreviations: AMS, acute maxillary sinusitis; AOM, acute otitis media; CAP, community-acquired pneumonia; UTI, urinary tract infection.

knowledge of the causative pathogen and where most respiratory infections, for example, are viral.

Clinical criteria for diagnosing infections varied between studies, which could impact on clinical outcome. This was particularly evident for *E. coli* UTIs, for which criteria for obtaining urine samples and diagnostic thresholds varied. Using a lower reference standard of $\geq 10^2$ CFU/mL and of $\geq 10^3$ CFU/mL and combining nitrite dipstick test results with clinical symptoms and signs improves diagnostic accuracy for UTI [S69] and, therefore, earlier treatment initiation and improved outcome [S70].

Although we applied a consistent approach associating resistance and sensitivity data to a specific antibiotic class, the class of treatment antibiotic was not always consistent with the class of antibiotic against which resistance was measured. This potentially overestimates clinical response failure associated with resistance to the specific antibiotic being used for treatment. Clinical response failures were more likely in both the main analysis and sensitivity analysis for *E. coli* UTIs and *S. pneumoniae* AOM but not sustained for the sensitivity analysis for *S. pneumoniae* CAP. We therefore cannot reach a robust conclusion that there was no greater likelihood of failure in resistant *S. pneumoniae* CAP compared with sensitive *S. pneumoniae*. Potential reasons for this may be the limited number of participants with CAP ($n = 91$), the low number of outcome events overall ($n = 11$), or that clinical criteria for CAP diagnosis were not reported in 1 of the 2 studies [31]. Data were limited for some infections (eg, skin or soft tissue) and secondary outcomes. It remains unclear whether other infections or bacteria have similar implications on patients' illness burden.

Implications for Practice, Policy, and Future Research

Clinically, our findings support the need to better identify patients who might need an antibiotic. By testing for antibiotic resistance through promoting and evaluating rapid diagnostics, we can avoid or reduce the risk of clinical response failure. Early evidence suggests that rapid diagnostics used in a community setting can guide antibiotic prescribing for CAP [S71], and trials are underway for UTIs [S72, S73].

Given that at least 1 in 3 women will experience a UTI during their lifetime [4] and that the incidence of UTI is approximately 0.5–0.7 per person-year [S74], our findings show that antibiotic resistance significantly impacts on patients' illness burden. We estimate that clinical response failure is almost 3 times more likely in patients with antibiotic-resistant *E. coli* UTIs and around 2 times more likely in patients with antibiotic-resistant *S. pneumoniae* CAP and AOM than in patients whose infections are antibiotic-sensitive based on our odds ratio estimate and median clinical response failure rate (*E. coli* UTI: relative risk = 2.96, OR = 4.19, median failure rate = 13%, range = 9%–32% [8, 32–34, 36–39]; *S. pneumoniae* CAP: relative risk = 1.97, OR = 2.15, median failure rate = 8%, range = 4%–50%

[29–31, 40, 41]; and *S. pneumoniae* AOM: relative risk = 2.18, OR = 2.51, median failure rate = 10%, range = 4%–16% [27, 31, 42, 45, 47]). Expressing the consequences of antibiotic-resistant infections in terms that are more meaningful to patients, among whom the concept of antibiotic resistance has been shown to be misunderstood [2], is important, especially where decisions about whether to start antibiotics may not be clear cut.

This impact may be much greater where the prevalence of antibiotic-resistant *E. coli* is higher (eg, in children with UTIs) [52]. Recent evidence reports that the global pooled prevalence of trimethoprim resistance used as first-line antibiotic treatment for *E. coli* UTI in children is 23.6% (range = 17.9%–30.3%) [52]. For more common illnesses like RTIs, the impact of antibiotic-resistant *S. pneumoniae* CAP in adults may be considerable because estimates vary considerably across European countries where approximately 1%–50% of *S. pneumoniae* isolates have been recorded as nonsusceptible to penicillin or macrolides [S75, S76].

A better grasp of the implications of antibiotic resistance on tangible outcomes may help curb patients' expectations for antibiotics [S77], facilitate shared decision making [S78], and inform more appropriate antibiotic prescribing behavior [S79] by informing guidelines, campaigns, and interventions to help healthcare professionals explain the potential implications of antibiotic-resistant infections in relation to outcomes that matter to patients.

More research is needed on the socioeconomic burden associated with antibiotic-resistant infections in the community, both in relation to direct healthcare resource utilization and indirect costs (eg, days off work) [S80]. Future work needs to develop a better understanding of the relationship between antibiotic prescribing levels and development of clinically significant antibiotic resistance in the community.

CONCLUSIONS

Antibiotic resistance has worse implications for patients' illness burden in the community. These findings could usefully inform better dialogue between clinician and patient, guidelines and campaigns about the benefits and risks of antibiotic treatment.

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

Acknowledgments. All authors have read the approved manuscript and agree to be answerable to all aspects of the work. O. V. H., K. W., and C. C. B. designed and led the research that contributed to the manuscript and were responsible for the main analysis. N. W., O. V. H. and K. W. designed and completed the literature search. O. V. H. and J. J. L. collected and extracted data. O. V. H., K. W., J. J. L., and C. C. B. were involved in appraising and interpreting the data, and all authors subsequently contributed to successive

drafts of the paper. The authors are grateful to Associate Professor Ann Van den Bruel for her helpful suggestions and critical reading of the manuscript, and Constantinos Koshariis for his statistical advice.

Disclaimer. The funding source was not involved in study design, data collection, analysis or interpretation, report writing, or submission for publication. The views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health.

Financial support. C. C. B. is supported in part by the Oxford NIHR Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance. The ARCHIE research programme (The early use of Antibiotics for “at Risk” CHildren with Influenza) is funded by the National Institute for Health Research’s (NIHR) Applied Research Programme. This publication summarizes independent research funded by the NIHR under its Programme Grants for Applied Research Programme (grant RP-PG-1210-12012).

Potential conflicts of interest. All authors: No reported 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. Simpson SA, Wood F, Butler CC. General practitioners’ perceptions of antimicrobial resistance: a qualitative study. *J Antimicrob Chemother* **2007**; 59:292–6.
2. McCullough AR, Parekh S, Rathbone J, Del Mar CB, Hoffmann TC. A systematic review of the public’s knowledge and beliefs about antibiotic resistance. *J Antimicrob Chemother* **2016**; 71:27–33.
3. Brookes-Howell L, Elwyn G, Hood K, et al. “The body gets used to them”: patients’ interpretations of antibiotic resistance and the implications for containment strategies. *J Gen Intern Med* **2012**; 27:766–72.
4. Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *Br J Gen Pract* **2015**; 65:e702–7.
5. Wood F, Simpson S, Butler CC. Socially responsible antibiotic choices in primary care: a qualitative study of GPs’ decisions to prescribe broad-spectrum and fluoroquinolone antibiotics. *Fam Pract* **2007**; 24:427–34.
6. de Kraker ME, Davey PG, Grundmann H; BURDEN study group. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med* **2011**; 8:e1001104.
7. de Kraker ME, Wolkewitz M, Davey PG, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. *J Antimicrob Chemother* **2011**; 66:398–407.
8. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with *E. coli* UTIs. *Br J Gen Pract* **2006**; 56:686–92.
9. Ashworth M, Latinovic R, Charlton J, Cox K, Rowlands G, Gulliford M. 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.
10. Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA* **2009**; 302:758–66.
11. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. *J Antimicrob Chemother* **2014**; 69:234–40.
12. MeReC. Urinary tract infection. *MeReC Bulletin* **1995**; 6:1–7.
13. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. *Vital Health Stat* **2011**; 1–38.
14. Hippisley-Cox J, Vinogradova Y. Trends in consultation rates in general practice 1995/1996 to 2008/2009: analysis of the QResearch® database. Final report to the NHS Information Centre and Department of health. Leeds, UK: NHS Information Centre for Health and Social Care, **2009**.
15. McCormick A, Fleming D, Charlton J. Morbidity statistics from general practice. Fourth National Study 1991–1992. London, **1995**.
16. Pallin DJ, Espinola JA, Leung DY, Hooper DC, Camargo CA Jr. Epidemiology of dermatitis and skin infections in United States physicians’ offices, 1993–2005. *Clin Infect Dis* **2009**; 49:901–7.
17. National Center for Health Statistics (US). Health, United States, 2010: with special feature on death and dying. Hyattsville, MD: Centers for Disease Control and Prevention, **2011**.

18. Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) Report 2014. London: Public Health England, **2014**.
19. Cals JW, Ament AJ, Hood K, et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *J Eval Clin Pract* **2011**; 17:1059–69.
20. Hollinghurst S, Gorst C, Fahey T, Hay AD. Measuring the financial burden of acute cough in pre-school children: a cost of illness study. *BMC Fam Pract* **2008**; 9:10.
21. Rosenberg M. Pharmacoeconomics of treating uncomplicated urinary tract infections. *Int J Antimicrob Agents* **1999**; 11:247–51; discussion 261–4.
22. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis* **2014**; 14:13.
23. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* **2010**; 340:c2096.
24. Gill PJ, Roberts NW, Wang KY, Heneghan C. Development of a search filter for identifying studies completed in primary care. *Fam Pract* **2014**; 31:739–45.
25. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions version 5.1.0. Higgins JPT, Green S, eds. The Cochrane Collaboration, **2011**. Available at: www.handbook.cochrane.org. Accessed March 2011.
26. Critical Appraisals Skills Programme (CASP). CASP checklists. **2013**. Available at: <http://www.casp-uk.net/>. Accessed 22 December 2015.
27. Barry B, Gehanno P, Blumen M, Boucot I. Clinical outcome of acute otitis media caused by pneumococci with decreased susceptibility to penicillin. *Scand J Infect Dis* **1994**; 26:446–52.
28. Buchanan P, Roos K, Tellier G, Rangaraju M, Leroy B. Bacteriological efficacy of 5-day therapy with telithromycin in acute maxillary sinusitis. *Int J Antimicrob Agents* **2005**; 25:237–46.
29. Hagberg L, Carbon C, van Rensburg DJ, Fogarty C, Dunbar L, Pullman J. Telithromycin in the treatment of community-acquired pneumonia: a pooled analysis. *Respir Med* **2003**; 97:625–33.
30. van Rensburg DJ, Fogarty C, Kohno S, Dunbar L, Rangaraju M, Nusrat R. Efficacy of telithromycin in community-acquired pneumonia caused by pneumococci with reduced susceptibility to penicillin and/or erythromycin. *Chemotherapy* **2005**; 51:186–92.
31. Zhanel GG, Wolter KD, Calciu C, et al. Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant *Streptococcus pneumoniae*: analysis of phase 3 clinical trial data. *J Antimicrob Chemother* **2014**; 69:2835–40.
32. McNulty CA, Richards J, Livermore DM, et al. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *J Antimicrob Chemother* **2006**; 58:1000–8.
33. Noskin GA, Zembower T, Chmielewski J, Tang P, La Rosa M, Peterson LR. Disappearance of the “uncomplicated” urinary tract infection—the impact of emerging resistance. *Clin Drug Invest* **2001**; 21:13–20.
34. Sørås A, Sundsfjord A, Jørgensen SB, Liestøl K, Jenum PA. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing *Escherichia coli*. *PLoS One* **2014**; 9:e85889.
35. Brown PD, Freeman A, Foxman B. Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. *Clin Infect Dis* **2002**; 34:1061–6.
36. Raz R, Chazan B, Kennes Y, et al.; Israeli Urinary Tract Infection Group. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clin Infect Dis* **2002**; 34:1165–9.
37. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med* **2007**; 167:2207–12.
38. van Merode T, Nys S, Raets I, Stobberingh E. Acute uncomplicated lower urinary tract infections in general practice: clinical and microbiological cure rates after three- versus five-day treatment with trimethoprim. *Eur J Gen Pract* **2005**; 11:55–8.
39. Vallano A, Rodríguez D, Barceló ME, et al.; Grupo de Estudio de las Infecciones del Tracto Urinario en Atención Primaria. Antimicrobial susceptibility of uropathogens and outcome following antibiotic treatment for urinary tract infections in primary health care. *Enferm Infecc Microbiol Clin* **2006**; 24:418–25.
40. O’Doherty B, Dutchman DA, Pettit R, Maroli A. Randomized, double-blind, comparative study of grepafloxacin and amoxicillin in the treatment of patients with community-acquired pneumonia. *J Antimicrob Chemother* **1997**; 40:73–81.
41. Yanagihara K, Otsu Y, Ohno H, et al. Clinical characteristics of pneumonia caused by penicillin resistant and sensitive *Streptococcus pneumoniae* in Japan. *Intern Med* **2004**; 43:1029–33.

42. Dagan R, Abramson O, Leibovitz E, et al. Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin. *Pediatr Infect Dis J* **1996**; 15:980–5.
43. Dagan R, Bar-David Y. Double-blind study comparing erythromycin and mupirocin for treatment of impetigo in children: implications of a high prevalence of erythromycin-resistant *Staphylococcus aureus* strains. *Antimicrob Agents Chemother* **1992**; 36:287–90.
44. Giordano PA, Elston D, Akinlade BK, et al. Cefdinir vs. cephalexin for mild to moderate uncomplicated skin and skin structure infections in adolescents and adults. *Curr Med Res Opin* **2006**; 22:2419–28.
45. Hoberman A, Dagan R, Leibovitz E, et al. Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. *Pediatr Infect Dis J* **2005**; 24:525–32.
46. Quinn J, Ruoff GE, Ziter PS. Efficacy and tolerability of 5-day, once-daily telithromycin compared with 10-day, twice-daily clarithromycin for the treatment of group A beta-hemolytic streptococcal tonsillitis/pharyngitis: a multicenter, randomized, double-blind, parallel-group study. *Clin Ther* **2003**; 25:422–43.
47. Hoberman A, Paradise JL, Block S, Burch DJ, Jacobs MR, Balanescu MI. Efficacy of amoxicillin/clavulanate for acute otitis media: relation to *Streptococcus pneumoniae* susceptibility. *Pediatr Infect Dis J* **1996**; 15:955–62.
48. Seppälä H, Nissinen A, Järvinen H, et al. Resistance to erythromycin in group A streptococci. *N Engl J Med* **1992**; 326:292–7.
49. Cao B, Zhao CJ, Yin YD, et al. High prevalence of macrolide resistance in *Mycoplasma pneumoniae* isolates from adult and adolescent patients with respiratory tract infection in China. *Clin Infect Dis* **2010**; 51:189–94.
50. Little P, Merriman R, Turner S, et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. *BMJ* **2010**; 340:b5633.
51. Kawai Y, Miyashita N, Yamaguchi T, et al. Clinical efficacy of macrolide antibiotics against genetically determined macrolide-resistant *Mycoplasma pneumoniae* pneumonia in paediatric patients. *Respirology* **2012**; 17:354–62.
52. Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ* **2016**; 352:i939.
53. Gagyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. *BMJ* **2015**; 351:h6544.
54. Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. *Scand J Prim Health Care* **2007**; 25:49–57.
55. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane Database Syst Rev* **2014**; 10:CD002109.
56. Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med* **2011**; 364:116–26.
57. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* **2015**; CD000219. doi:10.1002/14651858.CD000219.pub4.
58. Fahey T, Webb E, Montgomery AA, Heyderman RS. Clinical management of urinary tract infection in women: a prospective cohort study. *Fam Pract* **2003**; 20:1–6.
59. Little P, Turner S, Rumsby K, et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technol Assess* **2009**; 13:iii–iv, ix–xi, 1–73.
60. Farrell DJ, Morrissey I, De Rubeis D, Robbins M, Felmingham D. A UK multicentre study of the antimicrobial susceptibility of bacterial pathogens causing urinary tract infection. *J Infect* **2003**; 46:94–100.