Safety of reducing AB prescribing in primary care. Systematic new evidence from electronic health records

Summary of research

Background: Antimicrobial drug resistance (AMR) is a growing threat. Many antibiotic (AB) prescriptions in primary care are unnecessary and the NHS is now incentivising reduced AB prescribing in primary care. Reducing AB use too much might carry risks to patient safety if bacterial infections and their complications increase, potentially leading to hospital admissions and mortality, but very few studies have evaluated this possibility. Targets for reducing AB prescribing may need to distinguish variations in risk among population groups and different prescribing indications.

Objectives: This research aims to build on our previous research and provide the NHS with comprehensive new evidence concerning the safety of policies to reduce AB prescribing in primary care. This research asks whether it is safe to reduce AB prescribing in primary care? Is there a risk that bacterial infections might be more frequent if ABs are prescribed less often? If so, what is the safest way for the NHS to promote reduction of AB prescribing in primary care? We will investigate 'natural experiments' that will test the hypothesis that reducing AB prescribing in primary care might be associated with increased incidence of safety outcomes. We will develop and test new indicators for safe AB reduction in primary care.

Methods: There will be three work packages (WP):

WP 1: Epidemiological Study. We will systematically identify a comprehensive list of safety outcomes relevant to a policy to reduce overall AB utilisation in primary care. Case definitions will be developed. A cohort study will be conducted using electronic health records (EHRs) from the Clinical Practice Research Datalink (CPRD) with linked hospital episode, mortality and deprivation data. At population- (general practice-) level, we will estimate the incidence of each safety outcome by level of AB prescribing. At individual-level, we will conduct a series of epidemiological studies to evaluate relative and absolute risks of safety outcomes, allowing for confounding by indication using appropriate epidemiological methods. We will obtain estimates for the primary care population stratified by age-group, gender, comorbidity status, smoking, deprivation and, in older adults, frailty level using e-Frailty index. This research will extend our previous study by investigating a systematic listing of safety outcomes, including mortality and hospital admissions; extending the analysis to include all AB prescribing as well for different clinical presentations and patient risk groups; testing associations at the individual patient-level; and exploring risks in population sub-groups.

WP2: Modelling Study. There are trade-offs involved in reducing AB use. Benefits from reduced AB prescribing may be accompanied by small increases in risks to safety. In order to make these trade-offs explicit, we will construct a simulation model. Incidence estimates from EHR analyses will inform the model of the risks of infectious complications by pre-specified population sub-groups. The model will enable estimation of changes in numbers of safety outcomes per unit change in AB utilisation, contrasting universal versus targeted strategies for AB reduction.

WP3: Translational Study. The translational study will comprise two elements. An informatics stream will develop practice profiles of AB prescribing indicators and embed these into practice systems so as to inform clinical decision support during consultations. There will also be a qualitative interview study to explore how patients, prescribers and managers understand and respond to the research evidence from WP1 and WP2. What are their values and preferences with respect to safety issues in the context of AB prescribing? The qualitative study will also provide end-user feedback to the informatics stream.

Patient and public involvement: The idea for the study has been discussed with patients one of whom will join the study team as a co-applicant. A PPI group will meet quarterly to discuss and provide advice on the conduct of the study and to assist the team in ensuring that all results are presented in 'plain English'.

Dissemination: We will prepare a report and evidence summaries to communicate our results to policy makers at the Department of Health, National Institute for Health and Clinical Excellence, Public Health England and the NHS, represented on our Advisory Group. Our PPI group will input to this to ensure that our outputs clearly communicate our study findings. We will also aim to achieve academic impact through peer-review publications and conference presentations. The King's College London communications team will prepare press releases for new media. We also plan to make a series of professionally-produced short videos to communicate our findings to broad public audiences through social media including You Tube, Twitter etc.

Background and Rationale

The problem of antimicrobial drug resistance

The threat of antimicrobial drug resistance (AMR) is attracting the concern of national governments and international organisations. Margaret Chan, Director General of the World Health Organisation observed, 'We are hearing one alarm bell after another.' [1] Antibiotic-resistant infections are now increasing in frequency and are more often being identified in primary care when cultures are performed. The UK government has developed a five-year antimicrobial resistance strategy that identifies optimising prescribing practices as a key element of antimicrobial stewardship.[2] The emergence of AMR requires action from a range of sectors including the pharmaceutical industry, as well as in agriculture and food production, as outlined in the O'Neill Review.[3] But AMR has most immediate relevance in the health care sector, where antibiotics (AB) are prescribed and where patients with resistant infections are seen.

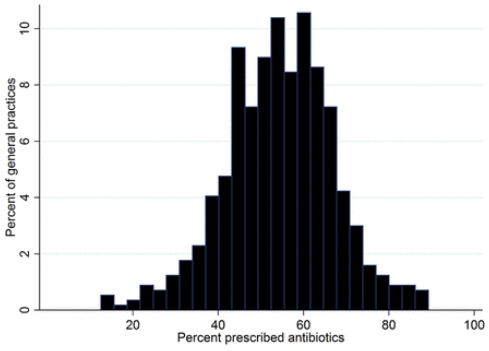


Figure 1: Distribution of proportion of RTI consultations with AB prescribed at 568 UK general practices.[4]

In the UK, primary care accounts for nearly three-quarters of all AB prescribing. Respiratory tract infections (RTIs) represent the largest single group of indications for AB treatment.[4] General practitioners prescribe ABs at an average of 52% of consultations for 'self-limiting' RTIs including common colds, acute cough and bronchitis, sore-throat, otitis media and rhinosinusitis,[5] with little change over the last two decades.[6, 7] [Figure 1]

The other main indications for AB prescription include urinary tract infections and skin infections, for which there may be less discretion concerning whether to use ABs, with greater emphasis given to appropriate AB selection.[4, 8] Analysis of electronic health records, shows that up to one third of all AB prescriptions in primary care in the UK may not be associated with specific diagnostic codes, possibly because GPs have recorded free-text information or recorded non-specific codes (such as 'had a chat with the patient'). [unpublished observations]

Evidence to support no prescribing strategies

Evidence from systematic reviews of randomised controlled trials shows that AB treatment for self-limiting RTIs generally has little if any effect on the severity or duration of symptoms and is commonly associated with unwanted symptomatic side-effects including rashes and

diarrhoea.[9, 10] Prescribing ABs also has the effect of medicalising conditions that are generally self-limiting and should be amenable to self-care. Patients given antibiotics for sore throat are 69% more likely to consult again for the same condition.[11] Consequently, UK NICE guidelines (currently being updated) recommend that a no AB prescribing, or delayed AB, strategy should be agreed with most patients presenting with self-limiting RTIs. [12] Respiratory conditions represent one of the most important opportunities to reduce antibiotic use.

Evidence that prescribing may be reduced

Several approaches are now being developed and tested to promote more effective AB stewardship in primary care. Deferred or delayed prescribing, in which a prescription is given but only used if needed, is sometimes advocated but this strategy may be less effective at reducing AB use while offering similar patient satisfaction to a 'no prescribing' strategy.[13] Algorithms are being developed to identify patients who may need antibiotics.[14, 15] Near patient testing for biomarkers of bacterial infection is being developed to enable targeted prescribing of ABs but this is not yet fully proven and may be difficult to integrate into usual clinical practice.[16] Behaviour change approaches as being tested. In one study in England, high prescribing general practitioners were sent an individualised letter signed by England's Chief Medical Officer, resulting in a 3% reduction in AB utilisation.[17] Finally, a contractual financial incentive, known as a 'Quality Premium', has been introduced into the English NHS for meeting indicative targets for year-on-year reductions in AB utilisation (Table 1).[18]

Table 1: Quality premium **indicators for AB prescribing in the NHS in England.[18]**

Year	Domain	Indicator
2017-19	Sustained reduction of inappropriate prescribing in primary care Reduction of inappropriate AB prescribing for UTI in primary care.	Items per STAR-PU must be equal to or below England 2013/14 mean performance value of 1.161 items per STAR-PU. This threshold will remain during 2018/19. 10% reduction (or greater) in the Trimethoprim: Nitrofurantoin prescribing ratio; 10% reduction (or greater) in the number of trimethoprim items prescribed to patients aged 70 years or greater.
2016-17	Reduction in the number of ABs prescribed in primary care.	4% (or greater) reduction on 2013/14 performance OR equal to (or below) the England 2013/14 mean performance of 1.161 items per STAR-PU Number of co-amoxiclav, cephalosporins and quinolones as a proportion of the total number of selected ABs prescribed in primary care to either: - to be equal to or lower than 10%, or - to reduce by 20% from each CCG's 2014/15 value
2015-16	Improved AB prescribing in primary and secondary care	reduction in the number of ABs prescribed in primary care by 1% (or greater) from each CCG's 2013/14 value. Number of co-amoxiclav, cephalosporins and quinolones as a percentage of the total number of selected ABs prescribed in primary care to be reduced by 10% or to below the 2013/14 median proportion for English CCGs (11.3%)

STAR-PU: Specific Therapeutic group Age-sex Related Prescribing Unit

Recently, attention has focused on evidence to support reducing AB utilisation in primary care. Based on international comparisons, with both low- [19] and high-[20] AB prescribing being observed across Europe without risks to patient safety, it appears that a substantial reduction of present AB prescribing in primary care might be reasonable. However, only a few existing research studies directly address the safety outcomes of reduced AB prescribing. A key aim of this proposed research is to provide the NHS with better evidence of the potential consequences for safety outcomes of reducing AB prescribing.

Giving AB treatment when needed

Strategies to reduce inappropriate use of ABs must ensure that ABs can be used when they are needed.[21] This is recognised in the NHS where reducing blood-stream infections is recognised as a key antimicrobial stewardship metric, alongside reducing inappropriate AB prescriptions.[18] Bacterial infections are still of public health importance with 123,000 cases of sepsis per year in England with 37,000 deaths.[22] Early recognition and treatment of sepsis is being promoted; some general practice systems are now incorporating 'sepsis alerts' that flag at-risk consultations. Reducing AB use might potentially compromise patient safety by increasing the risk of complications following minor infections that are expected to be self-limiting.[23]

The safety of reduced AB prescribing is a major concern for clinicians. One GP respondent commented: 'It's the fear of litigation or things going wrong, and if you have arbitrary targets like this . . . and I don't want to prescribe, but if it's needed, then pressure of some sort of appraisal and maybe being told off is not really needed.' [unpublished data] Parents are also concerned about safety issues, which are an important motivation for seeking active treatment for children.[24] Advice given by clinicians concerning 'safety-netting' may appear vague and unhelpful if patients are advised to re-consult 'if they are worried' or 'if [the patient] doesn't get better'.[24] A systematic review of qualitative studies found that clinicians commonly prescribe AB 'just in case' they might be needed.[25] There is a lack of research studies to provide quantitative estimates of risk that might allow clinicians to provide more evidence-informed advice.

Previous studies of safety outcomes of AB prescribing

Petersen and colleagues[26] reported a cohort study in 162 GPRD (General Practice Research Database) general practices from 1991 to 2001 showing increased odds of pneumonia after 'chest infection'; peritonsillar abscess after sore throat; and mastoiditis after otitis media. The absolute risks for these complications were generally low, with more than 4,000 AB prescriptions being required to prevent one case. However, in people over 65 years, one case of pneumonia might be prevented for every 38 'chest infections' treated with AB.

Little et al.[27] reported on a clinical cohort of 14,610 patients presenting with sore throat. Fewer than 1% had complications (including peritonsillar abscess, otitis media, sinusitis, impetigo or cellulitis). It was generally difficult to predict whether these complications might arise based on clinical features of the initial presentation.[28] In a cohort study, of patients with acute lower respiratory tract infection, Little et al.[29] found that hospital admissions and mortality were rare complications and these did not appear to be prevented by initial prescription of antibiotics.

Figure 2: Association of incidence of pneumonia and peritonsillar abscess with quartile of AB prescribing proportion. AB Propn: proportion of RTI consultations with AB prescribed at that general practice. Source: reference [23]

AB Propn. (%)	Events	IRR	95% CI	P value
	Pneumonia			
>=58	12042	0.70	0.59 to 0.82	<0.001
51 to 58	14602	0.74	0.63 to 0.87	<0.001
44 to 51	17843	0.98	0.83 to 1.15	0.80
<44	15303	Ref.		
	Peritonsillar			
>=58	1374	0.78	0.68 to 0.90	<0.001
51 to 58	1645	0.81	0.71 to 0.93	0.002
44 to 51	1741	0.90	0.79 to 1.03	0.11
<44	1716	Ref.		

Our group reported a study using data for more than 600 CPRD (Clinical Practice Research Datalink) general practices from 2005 to 2015.[23] Of the seven outcomes studied, we found that pneumonia and peritonsillar abscess were more frequent at general practices that prescribed ABs less frequently at consultations for self-limiting RTI (Figure 2). Absolute risks were small, with an average general practice experiencing one more case of pneumonia per year and one more case of peritonsillar abscess per decade for a 10% reduction in AB prescribing. However, these associations are of concern because hospital admissions for pneumonia have been increasing in the UK.[30] A report from New Zealand suggested that empyema (pus in the pleural cavity) has been increasing in children,[31] and whilst we found no association of practice-level antibiotic prescribing for RTI with incidence of empyema, mastoiditis, intracranial abscess, bacterial meningitis or Lemierre's syndrome (infective thrombophlebitis of the internal jugular vein) we cannot exclude there being small increases in risks.

Conducting this study highlighted uncertainty concerning the selection of relevant safety outcomes of RTI. Based on empirical evidence, members of the study team identified cellulitis as a complication of RTI,[28] but this was not accepted by journal reviewers who argued in turn that meningitis should be included as a safety outcome.

We know that a high proportion of health research findings cannot be reproduced.[32, 33] It is possible that previous research studies may have given either false positive or false negative safety signals. Our study[23] was based on general practice-level associations and though our results are plausible, consistent and show a dose-response relationship, it remains possible that associations may not hold at individual-level. It is important to confirm the findings of previous reports through more in-depth analysis using individual-level analysis and independent data sources.

Need for further research

The question of whether reducing AB prescribing carries risks to patient safety is clearly important but the evidence-base is currently extremely limited. Previous research raises several questions about the safety of reducing AB prescribing that require more systematic and thorough study:

1) as noted above, there is no consensus concerning the selection of relevant safety outcomes for study. Safety outcomes, and their case definitions, require more systematic investigation;
2) previous studies considered ABs prescribed for specific indications,[26] or for self-limiting RTIs,[23] but AB use for all indications should also be evaluated;
3) previous studies relied on primary care records, but validation from hospital episode data is desirable because differential code selection might occur in primary care in order to justify an AB prescription; [34]

4) mortality has not often been analysed as a safety outcome;
5) different age-groups require evaluation because these may have differing susceptibility to complications. Peritonsillar abscess (Quinsy) is most frequent in young adults, while pneumonia increases in frequency with age (Figure 3);
6) with the rapid increase in numbers of older people, the effects of frailty [35, 36] and comorbidity on susceptibility to complications in the most vulnerable require evaluation;
7) universal as compared to risk-stratified approaches to reduce AB prescribing require evaluation.

The present use of targets for global reductions in AB utilisation in the Quality Premium raises questions concerning the quality of the evidence available to inform target setting. Is a single target across all prescribing indications the optimal approach? Reducing AB utilisation may be more readily achieved in some groups of patients, and for some prescribing indications, than others. This research will contribute to developing of a set of indicators that will distinguish between different prescribing indications and different sub-groups of the population that vary in level of risk.

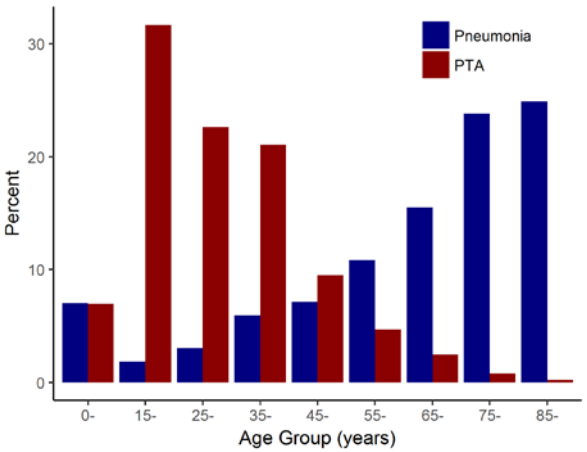
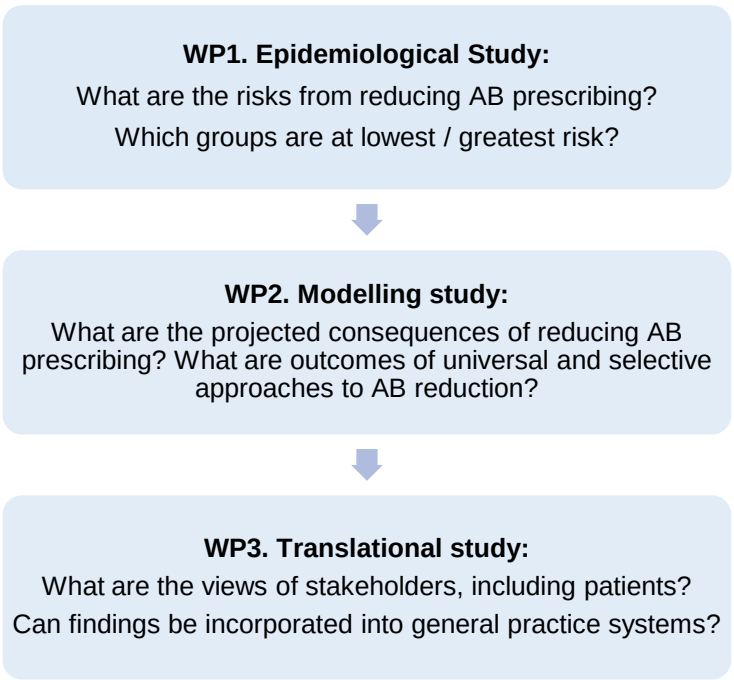


Figure 3: Age distribution of pneumonia and peritonsillar abscess (PTA). [unpublished data]

Our intention is that this proposed research will provide the NHS with a more systematic understanding of potential safety outcomes of reducing AB prescribing, thus enabling the identification of safer strategies for reducing AB utilisation. This research aims to answer important service delivery questions with respect to reduced AB prescribing in primary care. We intend to quantify the risks of a comprehensive and systematically identified list of safety outcomes; distinguish population sub-groups that may be at increased risk; estimate the expected number of safety outcomes associated with each unit reduction in AB prescribing.

Aims and Objectives

This research asks whether it is safe to reduce AB prescribing in primary care? Is there a risk that bacterial infections might be more frequent if ABs are prescribed less often? If so, what is the safest way for the NHS to promote reduction of AB prescribing in primary care? The research will specifically provide evidence concerning different prescribing indications and for different population groups based on risk stratification. The research will develop new indicators of safe and appropriate AB prescribing and will implement these into general practice systems.



The specific objectives are to:
1. Conduct an epidemiological study that will:
1.1) systematically identify a comprehensive list of safety outcomes relevant to policies for reducing overall AB utilisation in primary care;
1.2) conduct epidemiological analysis of electronic health records to estimate relative and absolute risks of each outcome in association with lower AB prescribing, based on both community-level and individual-patient level associations;
1.3) identify, for each safety outcome, risk groups in whom the incidence of the outcome may be highest (and lowest) and to estimate relative and absolute risks of AB prescribing or non-prescribing in these groups. The research will specifically evaluate sub-groups of age including children and older adults; gender; smoking; comorbidity, using the categories suggested by NICE; and, in very old people, level of frailty including 'fit', 'mild, 'moderate' and 'severe' frailty based on the e-Frailty Index;

2) construct a decision analysis model that will compare the consequences for safety outcomes of universal versus targeted policies to reduce AB prescribing in a large population;

3) engage with members of the public, patients and clinicians to understand their views and values in developing candidate indicators of safe AB prescribing reduction and implement these indicators into general practice information systems.

RESEARCH PLAN AND METHODS

The research will comprise a sequence of three work packages (Figure 4):

WP1) EPIDEMIOLOGICAL STUDY

We will conduct a series of epidemiological analyses to estimate the absolute and relative risks of a comprehensive list of safety outcomes in different population groups.

1.1. Definition of safety outcomes

Objective: to systematically identify a comprehensive list of morbidity and mortality safety outcomes, with case definitions, relevant to a policy to reduce overall AB utilisation in primary care.

Methods: We will review disease classifications (International Classification of Diseases, ICD-10; International Classification for Primary Care, ICPC-2; Read; and SNOMED). This will provide a comprehensive listing of all potential safety outcomes. We will then draw on epidemiological evidence from systematic literature reviews, expert opinion from the study team, the advisory group and the PPI group, to refine the selection of relevant safety outcomes for this research. Table 2 provides a summary of our approach. We will specifically include those outcomes analysed previously: pneumonia, peritonsillar abscess, mastoiditis, bacterial meningitis, intracranial abscess, empyema and Lemierre's syndrome. We also expect to include septicaemia, toxic shock syndrome, pyelonephritis, osteomyelitis, septic arthritis and Scarlet fever. We will also include as outcomes cause-specific mortality and hospital admissions from these conditions, using linked data for ascertainment.

Table 2: Preliminary list of safety outcomes potentially relevant to study.

Site	Infection	Complications
Respiratory	Common cold, sore throat, otitis media, rhinosinusitis, cough and acute bronchitis, 'chest infection'	Pneumonia, empyema,, peritonsillar abscess, mastoiditis, Lemierre's syndrome, intracranial abscess, cellulitis, impetigo
Genito-urinary	Urinary tract infection, cystitis, urethritis	Acute pyelonephritis, 'urosepsis'
Skin	Cellulitis, impetigo	Abscess
Other	Gallstones	Pyogenic liver abscess
Systemic complications		Sepsis, septicaemia (gram positive / gram negative), toxic shock syndrome, pyogenic arthritis, osteomyelitis, bacterial meningitis, Scarlet fever

Case definitions will be based on Read (primary care EHRs) and ICD-10 (HES and ONS mortality) classifications. We will compare our previous case definitions with those reported by Petersen et al.[26] Primary care prescribers may be selective in their use of codes; selection of codes varies between general practices and over time. Sensitivity analyses will be conducted to evaluate the effect of varying case definitions for key measures. We will also evaluate the extent to which antibiotic prescriptions may be issued without the recording of a specific diagnosis.

1.21 Data sources

Clinical Practice Research Datalink (CPRD): Epidemiological analyses will draw primarily on the Clinical Practice Research Datalink.[37] This is a database of primary care electronic records from 1990 to the present, with some 700 general practices contributing over time and about 300 presently active general practices. The CPRD population is considered to be representative of the UK population.[37] Data recorded includes coded data for medical diagnoses, drug

prescriptions, test results and referrals to secondary care. Many studies have reported that diagnoses recorded in CPRD are valid.[38]

Table 3: Outline of data sources available for study.

Outcomes	CPRD EHRs	Integrated HES	ONS-mortality	Alternate primary care HER sources (EMIS, ResearchOne)
Septicaemia				
etc				

Linked Hospital Episode Statistics (HES): to evaluate hospital admissions are available from CPRD for a sub-sample of 405 English CPRD general practices, using the Vision practice system, with a registered population of 10.2 million. Hospital episodes will initially be evaluated using ICD-10 codes recorded in 'integrated HES' available from CPRD at no additional cost. Following advice obtained from CPRD [enquiry reference 13571], we will also access 'basic HES' because the more detailed information held in basic HES will be required to distinguish between community-acquired and hospital-acquired pneumonia.
Linked ONS mortality statistics for all-cause mortality and cause-specific mortality are also available via CPRD for a similar number of English general practices.
Linked deprivation scores: General practice-level deprivation scores are available for all CPRD general practices, though different deprivation indicators – and different deprivation distributions - are used in the four countries of the UK. Deprivation scores based on individual level postcodes are available for selected general practices in England.
Alternative primary care databases, to test external validity in a second data source. This may include Research One data, drawing data from the TPP System One practice system and/or CPRD, which now offers access to data for practices using the EMIS practice system.

Data access: We presently have online access to CPRD. Under the terms of our licence we can request linked HES data and ONS mortality and deprivation data at no additional cost. We have agreement in principle to access Research One data.

1.22 Population stratification

A key aim of the research is to identify groups in the population that may be at greater risk of safety outcomes. We will consult with our PPI group to assess their views on appropriate subgroups. Analyses will consider sub-groups of *gender*; *age* (by ten-year age group); *frailty category* in those aged ≥65 years (including categories of 'fit', 'mild', 'moderate' and 'severe' frailty) based on the e-Frailty index[36], which we have coded into CPRD previously;[39] *comorbidity* using recognised indications for flu vaccination (seasonal flu 'at risk' Read codes[40]) as being present or absent; and *deprivation quintile*. Seasonal flu at-risk Read codes include diagnoses of significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis and young children born prematurely. Older adults are also considered at risk if they have diabetes, heart failure, current use of glucocorticoids or hospitalisation in the previous year. We will also evaluate *ethnicity* using Read codes recorded into CPRD, as reported in previous studies.[37]

We can estimate person time at risk by age-group and gender from the CPRD denominator file. We will need to additionally categorise the CPRD denominator file by comorbidity and frailty

category. This can be done running queries to determine the start date of comorbidity, or for each of the 36 conditions contributing to the e-Frailty index.

1.3 General practice-level analysis

Objective: To estimate relative and absolute risks for each outcome in association with lower AB prescribing, based on general practice-level associations; to identify, for each safety outcome, sub-groups in whom the incidence of the outcome may be highest (and lowest).

Design: Cohort study using approximately 600 UK CPRD general practices. Patients will be registered from 2002 to 2017, providing approximately 68 million person years of follow-up.[23] Cases will be evaluated as incident events of each outcome more than 12 months after the start of the participant's record.

Exposures: Rate of AB prescriptions (for all indications) per 1000 registered patients, for each general practice. AB prescribing rates for respiratory, skin, genito-urinary and unspecified indications will be evaluated in secondary analyses. Rates will be divided into quartiles for analysis (as shown in Figure 2).

Covariates/subgroups: Age-group, gender, comorbidity using codes defining eligibility for influenza vaccination, frailty category (e-Frailty index),[36] smoking status, [41] ethnicity, region and deprivation quintile as outlined above.

Outcomes: Safety outcomes as defined from section 1.1.

Sample size: There will be 68 million person years of follow-up, divided into four quartiles. The incidence of outcomes varies from more than 100 per 100,000 per year (pneumonia) to <1 per 100,000 per year (intracranial abscess).[23] Comparing lowest and highest quartiles there will be 80% power to detect relative risks of 0.97 for the more frequent outcome (pneumonia), and 0.71 for the rare outcome (intracranial abscess).

Analytical approach: We present the approach using septicaemia for illustrative purposes, with the other outcomes of interest being analysed in a similar framework. Initially, we will enumerate the number of first episodes of septicaemia in registered participants during a 15-year study period from 2002 to 2017. Practice-level analyses will be conducted with counts of septicaemia events aggregated by practice and five-year period, as well as by sub-groups of interest as outlined above. Incidence rates as absolute measures of risk will be compared across quartiles of AB prescribing. Adjusted incidence rate ratios will be estimated. Random effects Poisson models, with general practice as a random-effect, will be fitted to evaluate the association of septicaemia incidence with AB prescribing rate. The 'hglm' package[42] in the R program will be used.[43] We will evaluate the consistency of associations within sub-groups of age, gender, comorbidity and frailty.

Anticipated outcomes: This study will add to knowledge by evaluating a systematic list of safety outcomes and evaluating their association with general practices' AB prescribing for all indications, as well as sub-groups of AB prescribing for respiratory, genito-urinary, skin and other and unspecified indications. The risks of safety outcomes will be compared for important sub-groups of the general population. The study will use HES, ONS mortality data and EMIS or ResearchOne data for confirmatory analysis in independent data sources.

Limitations: We acknowledge several limitations of the data sources. General practices vary in their use of diagnostic codes leading to misclassification. While AB prescriptions issued by the practice will be comprehensively recorded, it may not always be clear whether a 'delayed' prescription has been issued (though 'post-dating' may sometimes be evident; delayed prescribing is less than 20% of total[27]); AB prescriptions from out-of-hours services may not be recorded. In spite of these limitations, our previous research shows that useful results may be obtained.[23] Evaluating multiple outcomes and investigating different population sub-groups can lead to problems associated with multiple testing. However, our focus will be primarily on estimation rather than hypothesis testing. Some of our outcomes represent independent hypotheses for which no adjustment for multiplicity is required; such as whether mastoiditis or pneumonia may be associated with reduced AB prescribing.[44] Where the incidence of a single outcome is compared for multiple population sub-groups, P-values will be corrected using appropriate procedures such as Bonferroni or Benjamini-Hochberg. A detailed protocol and analysis plan will be written in advance of data analysis which will pre-specify details of all sub-groups to be explored.

1.4 Individual-level analysis

Objectives: Individual-level analyses will aim to understand whether previous AB use may protect against the occurrence of safety outcomes for individual patients: i) what proportion of patients who experience a safety outcome, such as septicaemia, have consulted with their GP in the previous month? and ii) does an antibiotic prescription in the preceding month protect against the onset of the safety outcome?

Design: Drawing on the CPRD cohort analysed for 1.3, nested case-control studies will be conducted. Cases will be evaluated as incident events of each outcome more than 12 months after the start of the participant's record. Controls will be sampled from the set of patients that were registered with the same general practice on the case index date that had not previously been diagnosed with the outcome of interest, following Vinogradova et al.[45] Up to four controls per case will be sampled from the CPRD denominator file, individually matching for general practice, age and gender.

Exposures: i) consultation with the GP in the previous month (365.25/12 days), including broad sub-groups of conditions including respiratory, genito-urinary, skin, other, unspecified); ii) antibiotic prescription in the preceding month.

Covariates: Age-group, gender, comorbidity using the separate conditions that contribute to eligibility for influenza vaccination,[40] frailty category (e-Frailty index), [4] smoking status, [5] ethnicity, region and deprivation quintile as outlined above.

Outcomes: Safety outcomes as defined from section 1.1.

Sample size considerations: In unpublished interim analyses for the Data Monitoring Committee of the REDUCE Trial,[46] we found that 12.6% of pneumonia cases had RTI consultations within the preceding 21 days, with about half (6.3%) of these being associated with AB prescription. Using these data, together with numbers of cases identified previously, the study will have sufficient power to detect odds ratios above 0.8 or 0.9 for more frequent outcomes (e.g. pneumonia, peritonsillar abscess), though there will necessarily be less power to evaluate rare outcomes (e.g. intracranial abscess) (Table 4).

Table 4: Numbers of cases and odds ratios detectable (90% power, 5% significance, 4 controls per case) for protective effect of antibiotic.

Condition	Number of cases expected[23]	Odds ratio detectable
Pneumonia	59,790	0.93
Peritonsillar abscess	6,476	0.82
Mastoiditis	1,535	0.65
Intracranial abscess	190	0.19

Analytical approach: Adjusted odds ratios will be estimated using conditional logistic regression, adjusting for the covariates identified above. Sub-group analyses will be conducted as outlined above. Disregarding matching, the data can be set out as shown in Table 5.

Table 5:	**Cases**	**Controls**
Did not consult before index date		
Consulted, no AB prescribed		
Consulted, AB prescribed		

Anticipated outcomes: This study will contribute to understanding the antecedents of infective complications in general practice. Do complications arise in patients who have not previously consulted, or is it more common for patients to consult and receive (or not receive) antibiotic treatment before the onset of an infective complication? A population attributable risk fraction can be estimated.

Limitations and Additional Analyses: Confounding by indication may arise if patients who are destined to develop complications (safety outcomes) are more likely to consult and to be prescribed antibiotics. This will be addressed initially by regression adjustment for covariates. Additional analyses will explore the use of propensity scores in which analyses will explicitly evaluate features of patients' records that predict being prescribed antibiotics. This will enable us to conduct additional studies designed to compare outcomes for participants with similar propensity to be prescribed AB but who were or were not prescribed. We will also explore whether previous AB prescribing at the practice may be employed as an instrument in an instrumental variable analysis as described in CPRD data by Davies et al,[47] testing whether required assumptions are met.[48] We may also explore whether the self-controlled case series method – a design that compares different periods of time within participants - may be used to overcome between-person confounding.[49] However, there may be a risk of bias with this method if the occurrence of an outcome affects future risks of exposure.[50]

WP2. Modelling study: Population safety outcomes of different strategies to reduce AB prescribing

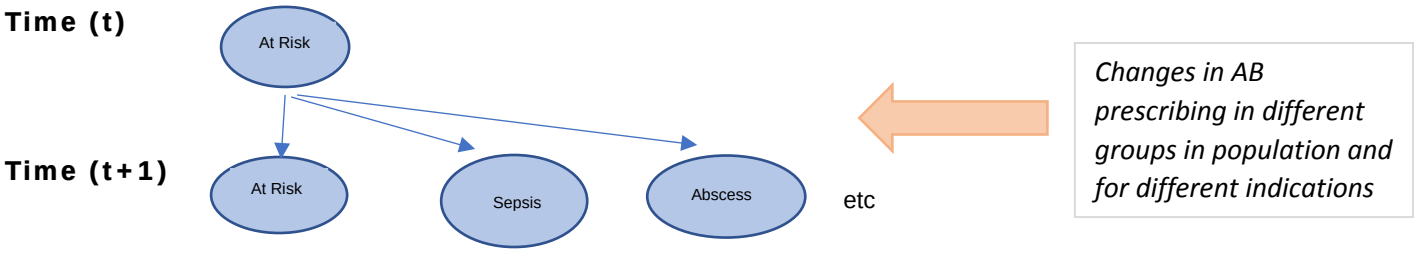
Purpose: In this part of the research, we will investigate the potential outcomes of reducing antibiotic prescribing either through a universal approach, or a targeted approach in which AB prescribing is selectively reduced in particular sub-groups of the population or for particular AB prescribing indications. We will do this by constructing a model to incorporate epidemiological estimates from WP1 for the incidence of safety outcomes for relevant population sub-groups as well as providing estimates of the relative risk of each outcome associated with quantified reduction in AB prescribing.

Objective: The objective of the modelling study is to identify strategies to reduce AB prescribing in a way that minimises any possible increase in safety outcomes.

Outcomes: Outcomes will be decrements in total AB utilisation and increments in safety outcomes. The outcome of the model will be incremental numbers of safety events (per 1,000 participants entering the model) per unit change in AB prescribing.

Interventions: A universal strategy for reduced AB prescribing will be contrasted with a targeted approach which distinguishes different groups of indications for AB treatment, and different population groups with varying levels of risk of safety events.

Figure 4: Outline of model.



Method: The purpose of the model is to obtain population-level estimates of numbers of safety events in relation to AB utilisation. A Markov model will be appropriate because we aim to estimate the outcomes of prescribing decisions for sub-groups of patients sharing similar characteristics (e.g. increased frailty), rather than evaluating outcomes of decisions for individual patients.

At baseline, the model will include a large population, divided into separate states according to age, gender and level of baseline risk, including smoking status, comorbidity, frailty status and deprivation. (This will draw on our experience of modelling for HSDR 12/5005/12 in which we produced a model stratified by year of age, gender, obesity category and deprivation). [6] In order to be policy-relevant, the model will evaluate changes over time horizons of five- and ten-years. (A lifetime time horizon is less relevant for this study because AB prescribing recommendations maybe expected to change over time.) The initial population will progress through annual cycles in which members of the cohort may experience safety outcomes or may progress to death. The effect of different AB prescribing strategies on safety outcomes and health care costs will be modelled using incidence and relative risk estimates obtained in WP1.

Model estimation

The probabilistic Markov model will be estimated by cohort simulation, implemented through a program written in R software,[43] drawing on our previous research.[51, 52]The start population entering the model will have the same distribution by age, gender, comorbidity, frailty and deprivation as in the CPRD sample. All simulations will be stratified by single year of age with the initial population aging by one year per cycle. The model will be run for each sex separately. Transition probabilities for incidence and mortality will obtained by sampling from the beta-binomial distribution, using CPRD data as inputs, as outlined by Briggs et al.[53] (p102).

Design of experiments

Outcomes will be compared for 'Intervention' and 'Usual Care' over five and ten annual cycles. 'Usual care' refers to continuing with present AB prescribing strategies – allowing for secular trends. 'Intervention' refers to a set of strategies for reducing AB prescribing (Table 5). The effects of 'Intervention' will be modelled using relative risk estimates drawn from the epidemiological study. We anticipate that intervention effects will be included as (log) relative risks and their standard errors, with values being sampled from a (log) normal distribution.[53]

Outcomes, in terms of total AB prescriptions and safety events, will be obtained by summing across the cycles of the model included in each simulation. There will be 1,000 simulations run for each of intervention or usual care scenarios. Results will be expressed as rates per 1,000 participants entering the model. Incremental changes in AB prescribing and safety outcomes will be obtained as the difference between 'Intervention' and 'Usual care' scenarios. Half-cycle corrections will be incorporated.

Table 5: Outline of simulation scenarios.

Scenario	Intervention
Usual care	To continue with present AB prescribing rates, allowing for secular trend
Universal strategy	To reduce AB prescriptions for all indications to a specified level, as exemplified by the English NHS Quality Premium target
Selective strategies	To reduce AB prescriptions by targeting those population groups and prescribing indications where AB prescribing can most safely be reduced. There may be more than one approach to a selective strategy. While the basis for selective strategies cannot be outlined in detail at the proposal stage, we expect that these strategies will draw on epidemiological data concerning population stratification (from 1.2) and evidence on prescribing indications (from 1.3)

We present an example in order to illustrate the intentions of the modelling study. If the population is divided into *i* age groups, 0-14, 15-24…85+, at current levels of antibiotic prescribing each group may have an underlying risk of pneumonia, $p_{i;}$ the relative risk of pneumonia associated with a specified reduction in antibiotic prescribing is estimated to be r_i; we also estimate risks of mortality with or without pneumonia, m_{ip}. We will use these estimates to model the year-on-year increment/decrement in key measures of safety outcomes and antibiotic prescribing, comparing universal as compared to selective intervention strategies. For example, knowing that antibiotic prescribing is greatest for children and old people, is it possible that a strategy that focuses on reducing lower risk groups at intermediate ages may be relatively safe but might have only modest impact on overall antibiotic utilisation? This might demonstrate a need for more selective prescribing strategies for younger and older people, which can be further evaluated through the modelling study.

The economic focus of the modelling study will be the estimation of costs of safety outcomes such as complications rather than the intervention costs associated with the hypothetical policy settings. The costs of prescribing antibiotics are generally fairly modest, while the health care costs of infective complications may be very high. The true costs of antimicrobial resistance are very difficult to evaluate because these might include, as Smith and Coast[54] point out, costs relating to the loss of much of modern healthcare. Consequently, the potential cost-effectiveness of different antibiotic prescribing strategies may be very difficult to evaluate, and are often under-estimated.

Sensitivity analyses: The model will be fully probabilistic and uncertainty in the inputs to the model will be carried through into the outputs of the model by sampling from appropriate probability distributions. In addition, sensitivity analyses will be implemented. These will vary key assumptions concerning the effects and costs of the intervention strategies, different case definitions etc.

Anticipated Outcomes: The modelling study will provide evidence concerning how AB prescribing can be reduced with least impact on safety outcomes. This will inform safe AB reduction for patients presenting with different conditions who are at lower risk of adverse outcome. This information will be translated into indicators that can be implemented into practice in WP3.

Limitations: We do not propose to implement a complete cost-effectiveness analysis because the benefits and costs of reducing (or not reducing) antibiotic prescribing, in terms of reduced (or increased) future impact of AMR, cannot be fully quantified and may accrue to populations outside of those represented in the model, as discussed by Smith and Coast.[54]

WP3: Translational study

Rationale: WP1 and WP2 will provide evidence that may be used to inform safe reductions in AB prescribing. This will comprise: i) a systematic list of safety outcomes of reduced AB prescribing; ii) case definitions for these outcomes; iii) identification of population subgroups that may be at higher/lower risk of particular outcomes; iv) quantitative estimates of risk; v) estimates from modelling of potentially safer strategies for reducing AB prescribing. In WP3, we will explore whether these tools can be translated into NHS settings through i) preliminary development of informatics tools that will enable incorporation into general practice systems; and ii) exploring the views and perceptions of the public, patients, clinicians and managers. These two components of the research will be conducted simultaneously and will be mutually reinforcing.

This research will complement existing antimicrobial stewardship resources from Public Health England (PHE) or the Royal College of General Practitioners, and those produced using aggregated AB prescribing data for general practices and CCGs. By analysing individual participant data, the research will distinguish different of levels of risk and different prescribing indications with a focus on safety outcomes of AB prescribing decisions.

3.1 Informatics study

Objective: To test the implementation of AB prescribing profiles from WP1 / WP2 into general practice systems in England.

Methods: We envisage that results from WP1 and WP2 will enable us to develop a profile of antibiotic prescribing for a general practice or CCG (Clinical Commissioning Group) population, together with a summary of AB-prescribing safety events. The profile will comprise a two-way classification of broad groups of conditions requiring AB prescription by population risk groups (based on age, gender, comorbidity, frailty and deprivation etc). The resulting table can be populated with metrics including AB prescribing rates, proportions of AB prescriptions in different categories and numbers of safety events. Where appropriate will use published weightings to convert registered populations into prescribing units (such as Specific Therapeutic group Age-sex Related Prescribing Units, STAR-PUs). 'Traffic-light' colour coding

will be utilised. For example, a high proportion of ABs prescribing for unspecified indications is generally considered a marker of sub-optimal practice.

Table 6: Outline of AB prescribing profile.

		Groups of conditions requiring AB prescription				
		Respiratory	**Genito-urinary**	**Skin**	**Other**	**Unspecified**
Population Risk Groups	**Age**					
	Gender					
	Comorbidity					
	Frailty					
	Deprivation					

We will test prototypes using data resources available in-house, including CPRD (with more than 300 presently active general practices from throughout the UK) as well as Lambeth DataNet (a collection of pseudonymised electronic health records from all 44 general practices in the London Borough of Lambeth).

We plan to develop methods to implement profiles into general practice systems including EMIS, TPP SystemOne and Vision. The informatics specialists in the team will develop appropriate data elements and represent these in software environments. We will use these to collect data both retrospectively and concurrently from the electronic health records of participating practices. We will draw on TRANSFoRm technology, including the semantic mediation approach using OpenEHR archetypes and the Clinical Data Integration Model. [55] Systems will be developed and embedded into EHR systems so that the AB prescribing profiles can be presented to prescribers. Starting from the TRANSFoRm model for representing the diagnostic process, the new systems will link to a dedicated evidence base storage, using a centrally maintained ontology to encode the AB prescribing indicators as a set of rules. Each tool will be embedded into an instance of an EHR (SystemOne, EMIS etc), connected to the evidence base, and equipped with a localised interface. We will collect metrics to track the short-term effects of the implementation in target practices, based on data collected in real-time using Web Improvement Support in Health (WISH) software platform for improvement data collection and reporting. This has been used in over 70 improvement projects and with over 1000 users. [56] Data to be collected will include rates of prescription of ABs for different population sub-groups, adherence with updated NICE recommendations and practices' use of the AB prescribing profiles.

Anticipated outcomes: This part of the research will develop a profile of indicators of safe AB reduction; it will also develop informatics tools that enable the representation of the profile in practice systems based on individual level data from patients' electronic health records.

3.2 Qualitative study

Objective: This part of the research will evaluate how patients, practitioners and managers understand and respond to the research evidence obtained in WP1 / WP2 and its implementation in WP3.1. What values and preferences do patients and prescribers hold concerning safety issues in the context of shared decision-making about AB prescribing? What are their perception of risks and what might help reassure them?

Methods: Semi-structured interviews will be conducted with a diverse sample of people who are registered with or working at general practices and CCGs in South London and Oxfordshire.

Participants: We plan to recruit 20-30 potential patients. There will be unrestrictive eligibility criteria because most people will have had experience of consulting for infection or seeking AB prescriptions either for themselves or for children or old people that they care for. A purposive sample will be recruited according to age, sex, whether a parent or carer, and level of comorbidity or frailty, and whether they had received an antibiotic prescription in the last 12 months. Eligible patients or carers will be identified from general practice registers. Invitations to participate in the study will be sent by the general practice on behalf of the research team.

We also plan to interview a sample of 20-30 health care workers. These will include GPs, practice nurses, pharmacists, practice and CCG managers, and CCG medicines management advisers from the same study areas. There will be at least five respondents in each of these categories. We intend that sampling will continue until no new themes emerge from the interviews.

Interview schedule: The interviews will be conducted by a research assistant who has been trained in qualitative data collection. Interview schedules guides will be developed for each group, informed by previous systematic reviews of qualitative research concerning AB prescribing, which have identified general concerns and views of patients and clinicians. [24, 25, 57, 58] Interview items will be guided by the Theoretical Domains Framework which was specifically developed to identify the cognitive, affective, social and environmental influences on the implementation of guidelines in healthcare.[59] We will develop a presentation, initially in Powerpoint, to present the results of epidemiological, modelling and informatics studies to respondents, alongside estimates from clinical effectiveness reviews. e.g.[10, 60] We will draw on well-established risk communication approaches to design clearly-presented estimates of absolute risk and numbers needed to treat / harm.[61, 62] We will also take advice from our PPI group concerning the content and style of the patient interview schedule and how best to present the results to patients. Interviews will be generally conducted face-to-face using a tablet computer to present materials. Interviews for health professionals may also be conducted over the telephone with online access to the presentation, according to individuals' preferences.

Qualitative analysis: Interviews will be digitally recorded with the participant's consent and fully transcribed. The Framework analysis approach to managing and classifying the data will be adopted because this research is addressing specific questions and a priori issues about AB prescribing.[63] The analytic framework will be developed to classify and organize the data according to key categories and sub-categories; key steps of analysis will include familiarization, developing a thematic framework, indexing, charting and interpretation.[63] These will be aided by the use of NVivo software.[64] The analytic framework will be developed to initially sort and categorize the data, based broadly on the domains encompassed by the interview schedule and Powerpoint presentation. All transcripts will be coded according to this framework. Each transcript will be coded according by one researcher and a 20% sample will be dual-coded by another member of the research team to ensure agreement about the categories derived from the data and whether selected data were representative of these.

Anticipated outcomes: This part of the research will inform the project of the values and preferences of patients and prescribers concerning safety issues in reducing AB utilisation.

Qualitative interview data will also contribute iteratively to the drafting of practice profiles for safe and appropriate AB prescribing for testing in 3.1.

Patient and Public Involvement: The proposal was discussed with three members of the public. Respondents agreed that this is an important topic for research, with potentially great impact on future generations. They considered that this topic is neglected by researchers at present even though it is very relevant for patients. Most people will have had experience of consulting with a general practitioner concerning the possibility of antibiotic treatment, either for themselves or as a parent or carer. The topic is potentially complex because there are benefits to patients from using antibiotic treatment as well as risks from either using or not using antibiotics. There may be growing public awareness that in future antibiotic treatment may no longer 'work' and this is an issue of concern. Consequently, there is a need to generate improved evidence that this research could provide.

PPI respondents agreed that inviting a group to advise the project would be the most appropriate means of providing PPI advice. The proposed group will comprise the principal investigator and the research assistant as well as four to six PPI representatives, including those named in the proposal. The size of the group will enable us to incorporate a diverse range of perspectives. Meetings will be held quarterly. Interim results from the project will be presented and discussed over a meeting of about 90 minutes. PPI input will inform the conduct of the project on an iterative basis. We expect that PPI input will be particularly relevant in the selection of safety outcomes (WP1.1), recognition of appropriate population sub-groups (WP1.2), interpretation of epidemiological and modelling analyses (WP1/WP2), and in the design of topic guide and presentation for patient interviews in WP3. PPI input will also contribute to dissemination by ensuring that communications are clearly expressed. PPI input will also inform the design of patient-facing materials from the project.

Gerry Bennison has agreed to join the team as a co-applicant to coordinate PPI input to the project. Gerry has acted in the role of lay member with the National Institute of Health and Care Excellence relating to diverse aspects of Health and Social Care. He also has previous experience in acting as a Fast Track Patient Research Reviewer for RDS London. Ettie Nicola, who is a member of the PPI Advisory Group at the NIHR Biomedical Research Centre (BRC) at Guy's and St Thomas' Hospital Trust (GSTT), has also agreed to participate in the PPI group. We plan to recruit two to four more members to the PPI group. We are able to access public and patient involvement (PPI) advice through the BRC at GSTT. The BRC PPI programme manager will engage in the project in order to facilitate public and patient input. PPI input to the project will include advice from people who have direct experience of problems of antibiotic resistance.

Approval by ethics committees: The CPRD has broad National Research Ethics Service Committee (NRES) ethics approval for observational research studies. The protocol for the proposed CPRD analyses will be submitted for scientific and ethical approval from the Independent Scientific Advisory Committee for CPRD studies. The modelling study does not require ethical approval. We will submit the protocol for WP3 to an NHS research ethics committee for review. We will also obtain all necessary NHS research governance approvals.

Dissemination and Projected Outputs: This proposed research has synergies with several current areas of policy or service activity. We are aware that the Department of Health is investigating targets for overall reductions in AB prescribing; the National Institute for Health and Care Excellence is developing new guidelines to help practitioners make better AB prescribing decisions; NHS Improvement is developing better tools to incorporate into practice management software. Consequently, there is potential for the evidence produced from this

research to inform policy and be rapidly implemented into the NHS and we have invited relevant participation into our Advisory Group.

We will aim to disseminate the results of the research to several different audiences in order to make them aware of this research and its potential for impact. ***Academic and professional audiences:*** through national and international academic and professional journal publications and conference presentations. ***Health services policy makers and managers:*** through end of project report, including executive summary; presentations at local and national meetings; professional journal publications (Health Services Journal); evidence summaries. The Department of Health, National Institute for Health and Clinical Excellence, Public Health England and the NHS at national, regional and CCG level may be key customers for this research. We have invited key stakeholders to join the project advisory group, where they can be updated regularly as well as informing the progress of the research. ***Public and patient audiences:*** we will prepare press releases, assisted by the King's College London communications team, and give interviews to print, online and TV/radio news media. This can be an effective way of communicating messages to a wide public audience. We will also use social media to assist in disseminating key findings. Our PPI group will help to draft patient summaries that can be disseminated to diverse patient audiences. We plan to make a series of professionally-produced short videos to communicate our findings to broad public audiences through social media including You Tube, Twitter etc. The PPI group will review these and evaluate their acceptability and appropriateness.

Anticipated outcomes: This research will contribute to ongoing research into antimicrobial stewardship at King's. We are presently completing a trial of electronically-delivered interventions to reduce antibiotic prescribing for self-limiting respiratory tract infections in primary care (HTA 13/88/10). Initial results suggest the need for interventions that are tailored to specific population groups and prescribing indications. We envisage that this HSDR project will enable us to refine intervention strategies by providing clearer evidence concerning when it is safe or not safe to manage patients without antibiotics. This evidence can be incorporated into future stratified (or personalised) interventions. We intend to evaluate the effectiveness of such interventions in future trials.