

**Do Antibiotic Stewardship Interventions in Primary Care Have an Effect on
Antimicrobial Resistance of *Escherichia coli* Bacteraemia in England? An Ecological
Analysis of National Data Between 2013-2018**

**Shirin Aliabadi, MPharm^{1*}, Philip Anyanwu, PhD^{1,2*}, Elizabeth Beech, BSc³, Elita
Jauneikaite, PhD^{4,5}, Professor Peter Wilson, MD⁶, Russell Hope, PhD⁷, Professor Azeem
Majeed, MD⁸, Berit Muller-Pebody, PhD⁷, Céire Costelloe, PhD¹**

Corresponding author: Dr Céire Costelloe

Tel: +44 (0) 20 7594 0799

Email: ceire.costelloe@imperial.ac.uk

¹ Global Digital Health Unit, Department of Primary Care and Public Health, School of Public
Health, Faculty of Medicine, Imperial College London, London, UK

² Centre for Medical Education, School of Medicine, Cardiff University, Cardiff, UK

³ NHS England and NHS Improvement, Wellington House, Waterloo Road, London, UK

⁴ Department of Infectious Disease Epidemiology, School of Public Health, Faculty of
Medicine, Imperial College London, UK

⁵ National Institute for Health Research Health Protection Research Unit in Healthcare
Associated Infections and Antimicrobial Resistance, Department of Medicine, Imperial College
London, Hammersmith Hospital, London, United Kingdom

⁶ Clinical Microbiology and Virology, University College London Hospitals NHS Foundation
Trust, London, UK

⁷ Division of Healthcare Associated and Antimicrobial Resistance, National Infection Service,
Public Health England, London, UK

⁸ Department of Primary Care and Public Health, Imperial College London, London, UK

Research in context

Evidence before this study

Financial rewards have been used to improve antimicrobial stewardship (AMS) in primary care settings with differing degrees of effectiveness. The Quality premium (QP) is a National Health Service (NHS) England intervention towards improvement in antibiotic prescribing. Implemented at clinical commissioning group (CCG) level, the QP included antibiotic optimisation in its 2015/2016 guidance with targets set each financial year towards reduction in the number of items prescribed in primary care. We searched PubMed for studies in English from 1st January 2000 to 1st January 2020 with the following search terms: ("antimicrobial stewardship" OR "antibiotic stewardship") AND ("primary care") AND ("antimicrobial resistance" OR "antibiotic resistance"). We reviewed the studies in order to identify relevant literature on the impact of AMS interventions in primary care on antimicrobial resistance (AMR). Studies evaluating the impact of the QP stewardship reward on antibiotic prescribing have shown reductions in the total number of antibiotics prescribed and antibiotic prescribing in primary care. One evaluation of the QP identified an 8.2% drop in the total number of antibiotics prescribed. Another study reported a 3% drop in rate of antibiotics prescribed for respiratory tract infections (RTIs) in particular. A further study noted that the reduction in antibiotic prescribing following the QP implementation was significantly higher amongst the top 20% of prescribers in England. However, none of these evaluations have included an assessment of the impact on AMR. Most evaluations of the impact of AMS interventions in England have focused on antibiotic prescribing rate as an outcome, with little evidence on their impact on AMR, which is a growing threat to global health security. Understanding the impact of such national interventions targeting antibiotic prescribing on resistance is important in quantifying the contributions of reduced prescribing to resistance trends, an area with limited evidence. A Scottish population-based study is one of the few evaluations of the impact of AMS interventions on AMR in the community. The study reported moderate reductions in resistance to three broad-spectrum antibiotics classes (fluoroquinolones, cephalosporins, and penicillins [co-amoxiclav]) among coliform bacteraemia. A further study conducted in Spain reported that implementation of AMS interventions in primary care improved appropriate antibiotic usage, reducing incidence of infections due to extended spectrum beta-lactamase (ESBL)-producing *E. coli* in the community.

Added value of this study

The study findings suggest that there were substantial reductions in community broad-spectrum antimicrobial prescribing associated on implementation of the 2015/16 QP AMS intervention. Corresponding changes in antimicrobial resistance amongst *Escherichia coli* bacteraemia, to all antibiotics individually and in combination, were more modest after

adjusting for confounding variables, including variations in general practitioner antibiotic prescribing. The present study has demonstrated that whilst the QP intervention has succeeded in reducing antibiotic usage, the corresponding resistance in *E. coli* causing bacteraemia, though attenuated following the implementation of the QP, remains on an upward trajectory.

Implications of all the available evidence

Whilst strategies to reduce inappropriate antibiotic prescribing can result in short-term reductions in resistance, these strategies alone may be insufficient alone in limiting the rise in AMR in the healthcare economy. Antibiotic prescribing in healthcare has been the cornerstone of antibiotic stewardship, but this is only one component of the stewardship landscape. It is becoming clearer that a leading cause of the unhindered resistance, despite falling antibiotic prescribing, is transmission of antibiotic resistance genes in the environment. It is therefore important to consider the impact of resistance genes and the patterns in which they are introduced into the population. It is discernible that a more radical, multi-sectorial approach, such as surveillance of resistance genes, is urgently needed to shift the growing threat of AMR. If we can identify the scale of genes that drive AMR, and how the bacterial population evolve and adapt to changing pressures of antibiotics, it will allow the development of targeted measures, diagnostics and treatments to prevent and control bacteraemia caused by resistant *E. coli*.

Summary

Background: We sought to evaluate the effectiveness of a national antimicrobial stewardship intervention, the Quality Premium (QP), on broad-spectrum antibiotic prescribing and *Escherichia coli* bacteraemia resistance to broad-spectrum antibiotics in England.

Methods: We used longitudinal data on patients registered with a general practitioner in the English National Health Service and patients with *E. coli* bacteraemia notified to the national mandatory surveillance programme between January 2013-December 2018. We conducted an ecological analysis using interrupted time series (ITS) analyses and generalised estimating equations (GEE) to estimate the change in broad-spectrum antibiotics prescribing over time and change in the proportion of *E. coli* bacteraemia cases where the causative bacteria were resistant to each antibiotic individually or to at least one of the five antibiotics, after implementation of the QP.

Findings: Following the implementation of the QP in April 2015, we observed an immediate downward step-change in broad-spectrum antibiotic prescribing incidence rate of 0.867 per 1000 patients (95% CI: 0.837 to 0.898, $p<0.001$). We found that the pre-intervention slope for total antibiotic usage was an IRR of 1.002 (CI: 1.000 to 1.004, p -value=0.046). The change in slope for total antibiotic usage was an IRR of 0.993 (CI: 0.991 to 0.995, $p<0.001$). We also observed a downward step-change in resistance rate of 0.947 per 1000 *E. coli* isolates tested (95% CI: 0.918 to 0.977, $p<0.001$). We found that the pre-intervention slope for total antibiotic resistance was an IRR of 1.001 (CI: 0.999 to 1.003, p -value=0.346). The change in slope level for total antibiotic usage was an IRR of 0.999 (CI: 0.997 to 1.000, $p=0.112$). On examination of the long-term effect following implementation of the QP, there was an increase in the number of isolates resistant to at least one of the five broad-spectrum antibiotics tested.

Interpretation: Whilst interventions targeting antibiotic use can result in changes in resistance over a short period, they may be insufficient alone in curtailing antimicrobial resistance.

Funding: National Institute for Health Research, Economic and Social Research Council (ESRC), Rosetrees Trust and The Stoneygate Trust.

INTRODUCTION

Antimicrobial resistance (AMR) is a persistent health issue causing approximately 700,000 deaths due to antibiotic resistant bacteria per year globally.¹ *Escherichia coli* (*E. coli*) is a frequent cause of bacteraemia, and accounts for 55% of all Gram-negative bacteraemia since 2017 in England.² The organism has become a particular concern due to its widespread antibiotic resistance.³ Inappropriate use of antibiotics is associated with the development and spread of antibiotic-resistant bacteria through promoting the selection of antibiotic-resistant strains⁴⁻⁷. In England, over 70% of antibiotics are prescribed in primary care, many of which are deemed inappropriate.⁸ To control AMR, antimicrobial stewardship interventions targeting antibiotic prescribing in primary care settings have been introduced.⁹

The Quality Premium (QP) is a National Health Service (NHS) England intervention which provided performance-related financial rewards to clinically-led statutory bodies, known as Clinical Commissioning Groups (CCGs), responsible for planning and commissioning local healthcare services.⁹ The scheme rewards CCGs for meeting annual targets. The QP included antibiotic optimisation as an antibiotic resistance indicator in its 2015/2016 guidance, with targets for CCGs to reduce both total antibiotic prescribing and broad-spectrum antibiotic prescribing (co-amoxiclav, cephalosporins, and quinolone items) each financial year.¹⁰

Studies evaluating the impact of antimicrobial stewardship interventions, such as the QP, have focussed on changes in antibiotic prescribing rate, with limited evidence on the subsequent impact of these on AMR.¹¹ Understanding the impact of such national interventions on AMR is important in quantifying the contributions of reduced prescribing to resistance trends. A Scottish population-based study by Hernandez-Santiago *et al.* is one of the few evaluations of the impact of antimicrobial stewardship interventions on AMR in the community, however, their analysis did not control for the possible effect of prescribing of antibiotics on AMR.¹¹

Five broad-spectrum antibiotics used to treat common infections in community practice as per the National Institute of Clinical Excellence (NICE) guidelines were investigated in this analysis.¹² The antibiotics included were co-amoxiclav, levofloxacin, ciprofloxacin, moxifloxacin and ofloxacin. This study used longitudinal data from 2013 to 2018 on prescribing and bacteraemia-causing *E. coli* resistance to these key antibiotics to fulfil two aims. These were to evaluate the effectiveness of the QP antimicrobial stewardship intervention on (i) broad-spectrum prescribing and (ii) resistance to broad-spectrum antibiotics, with adjustment for prescribing in primary care practices in England.

METHODS

Study design and setting

We conducted a quasi-experimental ecological study using monthly prescribing data from 6,882 GP practices in England from January 2013 to December 2018. The period covered offered an opportunity to investigate a 27-month pre-implementation of the QP period and a 45-month post-implementation of the QP period.

Data Sources and linkage

We used data on antimicrobial susceptibility testing (AST) of *E. coli* bacteraemia from the Communicable Disease Report (CDR) module of the Second-Generation Surveillance System (SGSS), a national microbiology surveillance database maintained by Public Health England (PHE). SGSS contained data on the patient's GP practice by linking the data to the NHS Spine¹³, a central repository containing information on patient demographics, which occurs on the day each specimen is reported to SGSS. We classified intermediate AST results as susceptible to reflect the latest European Committee on Antimicrobial Susceptibility (EUCAST) definitions for AST.¹⁴ We linked the SGSS data to data from the mandatory surveillance scheme, a data reporting and analysis system for surveillance of healthcare-associated infections (HCAI) at PHE, to confirm the onset location of each episode of bacteraemia using an apportionment algorithm.² The *E. coli* bacteraemia AST results were clustered at the unit of GP practice level using the patient's GP practice code. We obtained monthly practice-level antibiotic prescribing data from OpenPrescribing, an Evidence-Based Medicine DataLab project at the University of Oxford,¹⁵ and subsequently linked this to the SGSS data using the GP practice code. Data from OpenPrescribing were obtained from the NHS Business Services Authority (NHS BSA) prescribing and dispensing information systems.¹⁶

Based on previous ecological studies which have examined population-level changes in antibiotic prescribing and resulting resistance, changes in antibiotic prescribing at a GP practice level were assumed to have an impact on antimicrobial resistance associated with *E. coli* bacteraemia within 6 months.⁴ A 6-month lag period was therefore computed when linking the prescribing dataset and the *E. coli* bacteraemia AST results to account for this delayed impact. The final linked dataset included monthly counts of resistant isolates for each antibiotic and the monthly count of usage of each antibiotic per practice (see Figure 1 for a flowchart of data linkage).

Model generation and outcomes

We examined prescribing trends of the five broad-spectrum antibiotics individually and as an aggregate. We examined resistance trends in *E. coli* isolates causing bacteraemia following the implementation of the QP. A binary variable was created to denote resistance to at least one of the five commonly prescribed broad-spectrum antibiotics (co-amoxiclav, ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin). All analyses were conducted at the unit of the GP practice level. The main predictor was a binary variable indicating the implementation of the 2015/16 QP. The intervention period included April 2015 to December 2018 with the pre-intervention period as a control. The number of months since 2015/16 QP implementation was used to examine long term changes in trend following the intervention until the end of the study period.

Confounders and effect modifiers in this study included the Index of Multiple Deprivation (IMD) from the English Indices of Deprivation 2015, based on the GP practice postcode.^{17,18} The IMD is a numeric relative measure of deprivation based on information from seven domains. These seven domains are income, employment, education, skills and training, health and disability, crime, barriers to housing services and living environment.¹⁸ The geographical region of each practice was also included as a potential confounder, defined by PHE centre. These centres were North East, North West, Yorkshire and the Humber, East Midlands, East of England, West Midlands, South East, South West and London.¹⁹ Additionally, prevalence of comorbidities and age distribution will affect the rate of antibiotic prescribing and will vary across practices.²⁰ We therefore adjusted models for proportions of patients between 0-14 and over 65 years,²¹ and the yearly prevalence of asthma, chronic obstructive pulmonary disease (COPD), diabetes, cancer, and chronic kidney disease (CKD) per 100 patients.²² We linked these data to the prescribing and *E. coli* bacteraemia AST results using a unique identification code for each GP practice.

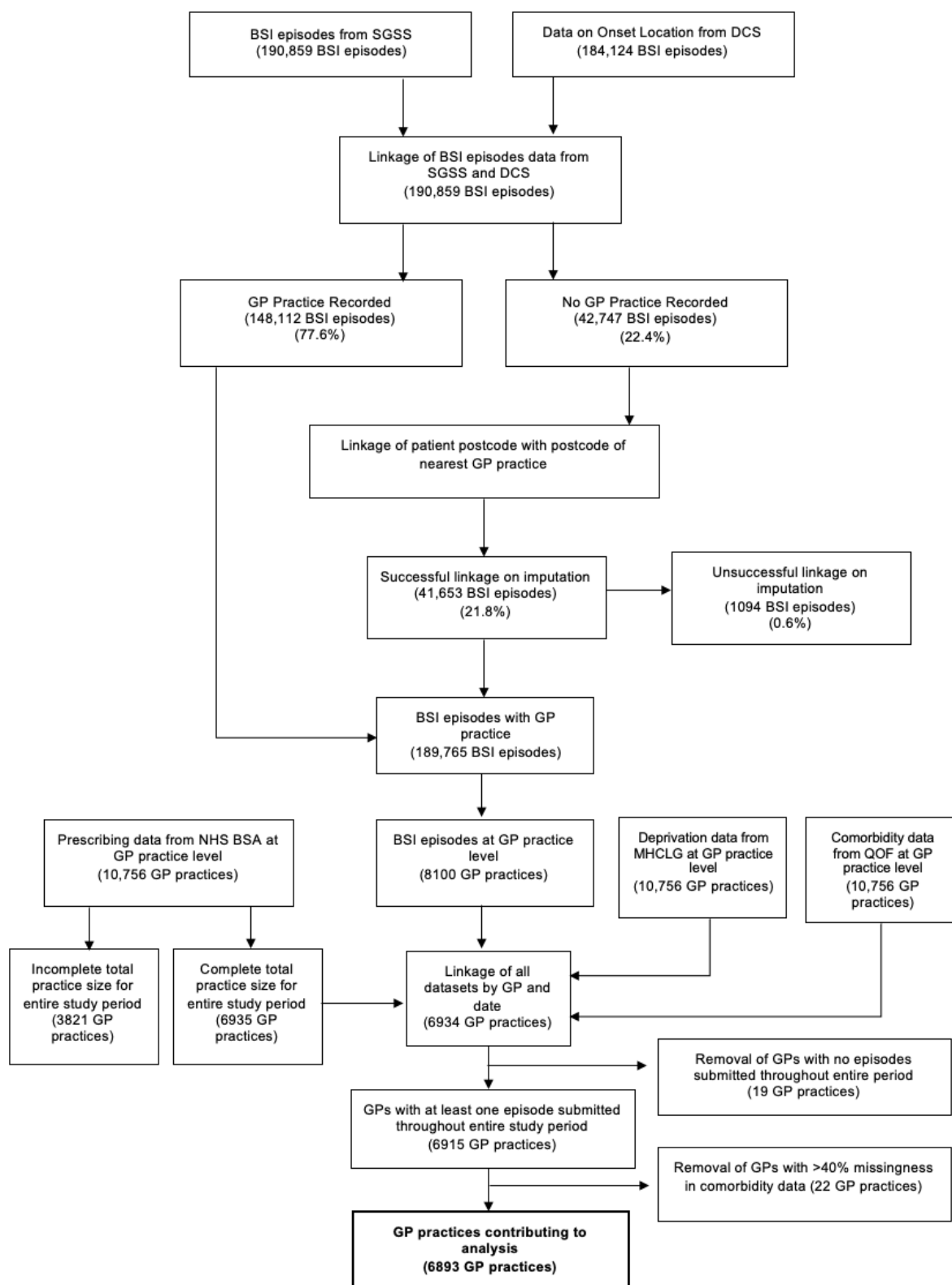


Figure 1. Flowchart for dataset creation and linkage

Abbreviations: BSI – Bloodstream Infection; DCS – Data Capture System; GP – General Practitioner; QOF – Quality and Outcomes Framework; MHCLG - Ministry of Housing, Communities and Local Government

Statistical analysis

Interrupted time series (ITS) is a powerful quasi-experimental method for evaluating the longitudinal effects of public health intervention.²³ We used ITS to estimate changes in the rate of antibiotic prescribing and *E. coli* resistance to antibiotics over time following the implementation of the 2015/16 QP. We examined changes in trends of *E. coli* resistance as a change in the rate of resistant community-onset *E. coli* bacteraemia isolates per 1000 isolates tested per month. The offset for this outcome was the total number of isolates that were tested against the antibiotic during AST. We examined changes in trends of prescribing of antibiotics as a change in the rate of antibiotic prescriptions per 1000 patients per month. The offset for this outcome was total number of patients registered at the GP practice. The outcomes were assessed by generalised linear regression analysis of the time series, aggregating the outcomes for each month and including the offset. We examined changes in trends for pre-intervention trends, changes in level after the QP implementation and changes in slope for post-intervention trends. The regression coefficients obtained from ITS models were exponentiated to obtain incidence rate ratios (IRRs). A trend line denoting the counterfactual scenario was generated. This was the predicted trend that would have been expected had the QP not been implemented. This trend line was compared to the observed post-intervention trend line. Absolute changes were calculated by taking difference between the predicted pre-intervention trend of the outcomes and the actual trend at the end of the study period. We evaluated the relative change by calculating the absolute change as a relative proportion.

We tested the data for overdispersion by comparing the Akaike Information Criterion (AIC) of the negative binomial and Poisson regressions. Models were selected where the model fit improved, denoted by a lower AIC. All models were a priori adjusted for season by adding a the 'month' variable, due to the accepted assumption that antimicrobial prescribing and resistance differ by season.^{24,25} To assess autocorrelation, we inspected the residual, autocorrelation (ACF) and partial autocorrelation function (PACF) plots (Supplementary Figures 1 and 2). We also used the Durbin-Watson test to examine first order autocorrelation. Where we noted autocorrelation, we added lag terms to the models. As the data were at monthly level, any significant lags up until 12th-order were chosen for further analyses. In order to assess whether the lag term should be included in the final model, we assessed whether the addition of the lag term (i) improved the Durbin-Watson statistic (ii) was statistically significant in the model (iii) improved model fit on comparing the AIC of the models and using likelihood ratio tests (iv) indicated residual autocorrelation on implementing the Breusch–Godfrey test.

We used generalized estimating equations (GEE) with ecological resistance data at GP practice level clustered by time (month) to predict the impact of QP on antibiotic resistance. The Poisson variance was used for GEE models. The GEE method accounts for overdispersion due its basis in quasi-likelihood.²⁶ Models with resistance as the outcome used total number of isolates submitted per month as an offset. A continuity correction of 0.5 was added across all variables related to resistance to enable total isolates in the offset. Models with antibiotic usage as the outcome used total number of patients per month as an offset. A continuity correction of 0.5 was also added to variables related to usage. The correlation structure was assessed using the Quasi-Information Criterion (QIC) and the model with the lowest QIC was chosen. We adjusted the GEE models to take into account prescribing rates of included antibiotics, the proportion of patients above 65 years old and between 0-14 years old in each practice, PHE region, season, deprivation level and prevalence of the comorbidities. The regression coefficients obtained from GEE models were exponentiated to obtain incidence rate ratios (IRRs).

We used R Studio (<http://www.r-project.org>) for data management and ITS analysis using the 'glm' and 'glm.nb' functions in the MASS package. We used Stata version 14 (Stata Corp, College Station, TX, USA) for modelling GEE using the 'xtgee' function.

Missingness and sensitivity analyses

GP practices that did not meet analysis criteria were excluded (Figure 1) and imputation methods were employed to address missingness. Where comorbidity data was missing for individual months, we used the last observation carried forward (LOCF) method.¹⁷ We manually imputed missing GP practice IMD scores using the practice postcode (n=24). We used the patient's registered GP practice for the vast majority of practices. Where GP practice code was missing, we imputed GP practice from those closest to patient address using the first three letters of the patient postcode. We conducted three sensitivity analyses. Firstly, we conducted a sensitivity analysis using GEE, using the dataset with only complete GP practice codes and compared effect sizes across models with imputed versus fully observed datasets. Second, we conducted a further sensitivity analysis using GEE to compare the effect of the QP in different GP practice types. A binary variable was created to denote the top 20% of GP practices that observed the largest decreases in prescribing following the implementation of the QP, with the remaining 80% of GP practices as the baseline of this variable. The variable was then added as an interaction term in the GEE model comparing effect sizes across the practice types. Finally, in order to investigate extended spectrum beta-lactamase (ESBL)-producing isolates,²⁷ we conducted a further sensitivity analysis. ESBLs are enzymes produced by bacteria that confer resistance to broad spectrum antibiotic classes such as those

included in this study. We therefore conducted a standalone ITS analysis for the third-generation cephalosporin ceftriaxone as ceftriaxone-resistant *E. coli* are a known proxy for identifying ESBL producing isolates.²⁷ Ceftriaxone antimicrobial susceptibility testing (AST) data was obtained from the Communicable Disease Report (CDR) module of the Second-Generation Surveillance System (SGSS).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Descriptive analysis results

The total number of prescriptions issued over the study period for all five antibiotics was 7,002,756 (760,497 ciprofloxacin, 6,068,217 co-amoxiclav, 82,500 levofloxacin, 29,953 moxifloxacin and 61,589 ofloxacin). Over the study period (72 months), the mean number of antibiotics prescribed per GP practice was 1017.55 (SD = 816.35, 95% CI: 998.26-1036.84) (Table 1). Supplementary Table 1 shows the mean number of items for the entire pre- and post-intervention periods.

Table 1. GP practice antibiotic prescribing for community-onset *E. coli* bacteraemia isolates

	Antibiotics prescribed over the entire study period (Jan. 2013 to Dec. 2018, 72 months) (n = 6,882 ¹)				Antibiotics prescribed in the 6-month period before implementation of QP (Oct. 2013 to Mar. 2015) (n = 6,882 ¹)				Antibiotics prescribed in the 6-month period after implementation of QP (Apr. 2015 to Sep. 2015) (n = 6,882 ¹)			
	Mean	SD	Lower 95% CI	Upper 95% CI	Mean	SD	Lower 95% CI	Upper 95% CI	Mean	SD	Lower 95% CI	Upper 95% CI
Ciprofloxacin	110.51	116.46	107.75	113.26	10.79	13.22	10.48	11.10	9.38	11.34	9.11	9.64
Co-Amoxiclav	881.75	737.71	864.32	899.18	86.59	81.30	84.67	88.51	73.63	67.79	72.03	75.24
Levofloxacin	11.99	36.71	11.12	12.86	0.99	3.75	0.90	1.08	0.86	3.33	0.78	0.94
Moxifloxacin	4.35	12.53	4.06	4.65	0.39	1.61	0.35	0.43	0.34	1.43	0.30	0.37
Ofloxacin	8.95	15.94	8.57	9.33	0.59	1.56	0.56	0.63	0.59	1.55	0.55	0.62
Total Antibiotics	1017.55	816.35	998.26	1036.84	99.35	88.15	97.27	101.43	84.79	74.35	83.04	86.55

Abbreviations: CI = Confidence Interval, SD = standard deviation

¹ Number of GP practices included in study as the denominator

We included practices that had complete observations for the variable on the number of patients in the practice for the 72 months covered in this study; this represents 99.3% of GP practices in England as of December 2018.²¹ We included data for 99.3% of the 6,928 GP practices in England as of December 2018, which is the last month of observation in our dataset. The remaining 0.7% (46) of practices did not have complete observations for preceding months in our study (for instance, practices that opened or closed during the observation period).

A total of 138,787 *E. coli* bacteraemia isolates were recorded over the study period (Supplementary Table 2). Of these, 84,078 (60.6%) *E. coli* isolates were susceptible to all five antibiotics included in the study, and 54,709 (39.4%) *E. coli* isolates were resistant to at least one of the five antibiotics. Of all isolates, 74,519 (53.7%) were recovered from female patients. The highest number of isolates came from those who were 65 years and over (72.5%). The South East region of England had the highest number of isolates submitted (15.6%) whilst the North East region contributed the lowest (6.5%). A total of 119,140 isolates were tested for resistance to co-amoxiclav whilst only 112 were tested against ofloxacin (Supplementary Table 2).

ITS analysis results

A time series plot showed an overall reduction in the sum prescribing of all five broad-spectrum antibiotics over the study period. After the implementation of the QP, the ITS analysis showed an immediate downward step-change in the prescribing rate of the broad-spectrum antibiotics (IRR of 0.867 per 1000 patients, 95% CI: 0.837 to 0.898, $p < 0.001$). The pre-intervention slope for total antibiotic usage was an IRR of 1.002 (CI: 1.000 to 1.004, p -value=0.046). The change in slope level for total antibiotic usage was an IRR of 0.993 (CI: 0.991 to 0.995, $p < 0.001$). This was an absolute change of 0.870 and a relative change of -56.50%. Similar trends and changes in trends were observed for most of the antibiotics when plotted individually. Over the study period, there was an increasing trend in resistance rate to broad-spectrum antibiotics, which was attenuated following the implementation of the QP. ITS analysis showed there was an immediate downward step-change in the rate of resistance (IRR of 0.947 per 1000 isolates tested; 95% CI: 0.918 to 0.977; $p < 0.001$) following the implementation of the QP. The pre-intervention slope for total antibiotic resistance was an IRR of 1.001 (CI: 0.999 to 1.003, p -value=0.346). The change in slope level for total antibiotic usage was an IRR of 0.999 (CI: 0.997 to 1.000, p =0.112). The absolute change at 35.44 and the relative change was -12.03%.

After the implementation of the QP, the ITS analysis showed there was no change in the rate of ciprofloxacin prescribing (IRR of 1·009 per 1000 patients, 95% CI: 0·996 to 1·022, $p=0\cdot198$) however there was a down-ward step change in co-amoxiclav prescribing (IRR of 0·866 per 1000 patients, 95% CI: 0·835 to 0·897, $p<0\cdot001$). The increasing trend in co-amoxiclav resistance seen over the study period attenuated following QP implementation. ITS analysis showed an immediate downward step-change in resistance rates for both antibiotics after QP implementation (ciprofloxacin: IRR of 0·939 per 1000 patients, 95% CI: 0·887 to 0·993, $p=0\cdot028$ and co-amoxiclav: IRR of 0·942 per 1000 patients, 95% CI: 0·908 to 0·978, $p=0\cdot039$).

The QP had no impact on moxifloxacin prescribing (IRR of 0·951 per 1000 patients, 95% CI: 0·899 to 1·005, $p=0\cdot860$) and resistance (IRR of 0·942 per 1000 patients, 95% CI: 0·887 to 1·339, $p=0\cdot740$).

Over the study period, there was an increasing trend in levofloxacin prescribing. An attenuation of the trend in levofloxacin prescribing was seen after QP implementation (IRR of 0·928 per 1000 patients; 95% CI: 0·890 to 0·968; $p<0\cdot001$). The QP had no impact on ofloxacin prescribing at QP implementation (IRR of 1·008 per 1000 patients; 95% CI: 0·969 to 1·050; $p=0\cdot680$). The QP had no impact on levofloxacin and ofloxacin resistance although there was a low number of isolates reported for these antibiotics and months with no isolates reported (see Table 1). All ITS coefficients are shown in Table 2 and corresponding plots are shown in Figure 2. Residual diagnostics are found in supplementary Figures 1 and 2.

Table 2. Interrupted time series analysis of changes in trends for antibiotic usage and antimicrobial resistance

	Regression intercept	Pre-intervention trend	Immediate change after implementation of the QP	Change in trend over study period	Absolute effect	Relative effect (%)
Antibiotic Usage^a						
Total Antibiotic Usage	0.002 (0.002 to 0.002)	1.002 (1.000 to 1.004)	0.867 (0.837 to 0.898)	0.993 (0.991 to 0.995)	0.870	-56.50
Co-amoxiclav	0.002 (0.002 to 0.002)	1.003 (1.001 to 1.005)	0.866 (0.835 to 0.897)	0.992 (0.990 to 0.994)	0.842	-62.68
Ciprofloxacin	0.000 (0.000 to 0.000)	0.999 (0.999 to 1.000)	1.009 (0.996 to 0.914)	0.997 (0.996 to 0.997)	0.020	-15.26
Levofloxacin	0.000 (0.000 to 0.000)	1.008 (1.006 to 1.010)	0.928 (0.890 to 0.968)	1.000 (0.997 to 1.002)	0.003	-8.71
Ofloxacin	0.000 (0.000 to 0.000)	0.999 (0.998 to 1.001)	1.008 (0.969 to 1.050)	1.001 (0.998 to 1.004)	0.001	5.30
Moxifloxacin	0.000 (0.000 to 0.000)	1.001 (0.998 to 1.004)	0.951 (0.899 to 1.005)	0.998 (0.995 to 1.001)	0.000	-5.68
Antimicrobial Resistance^b						
Total Antimicrobial Resistance	0.226 (0.207 to 0.246)	1.001 (0.999 to 1.003)	0.947 (0.918 to 0.977)	0.999 (0.997 to 1.000)	35.44	-12.03
Co-amoxiclav	0.356 (0.341 to 0.373)	1.004 (1.003 to 1.006)	0.942 (0.908 to 0.978)	0.998 (0.996 to 1.000)	72.25	-17.56
Ciprofloxacin	0.170 (0.159 to 0.181)	1.000 (0.998 to 1.003)	0.939 (0.887 to 0.993)	1.003 (1.000 to 1.006)	10.43	5.66
Levofloxacin	0.134 (0.102 to 0.178)	0.999 (0.988 to 1.009)	0.994 (0.813 to 1.241)	0.995 (0.983 to 1.006)	63.01	-27.63
Ofloxacin	0.777 (0.147 to 4.123)	1.009 (0.952 to 1.070)	1.062 (0.503 to 2.244)	0.988 (0.928 to 1.051)	566.03	-64.29
Moxifloxacin	0.231 (0.100 to 0.534)	1.003 (0.974 to 1.032)	0.942 (0.663 to 1.339)	0.995 (0.965 to 1.026)	77.59	-29.81
Confidence intervals shown in brackets						
Incidence Rate Ratios (IRR) were obtained by Poisson or Negative Binomial regression analyses						
^a As a change in rate of antibiotics prescribed per 1000 patients in GP practice						
^b As a change in rate of resistant isolates per 1000 isolates submitted to Public Health England						

422

423

424

425

426

427

428

429

430

431

432

433

434

435

436

Antibiotic prescribing

All Antibiotics

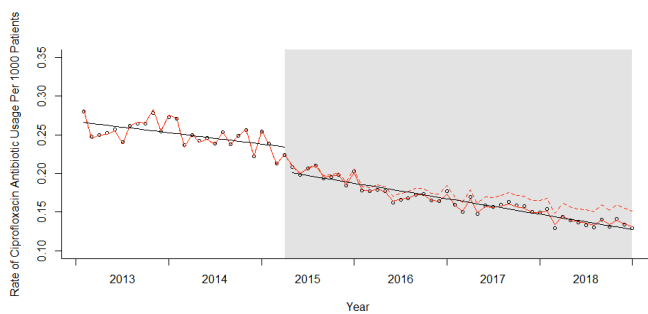


Antibiotic Resistance

Rate of Total Antibiotic Resistance Per 1000 Isolates



Ciprofloxacin



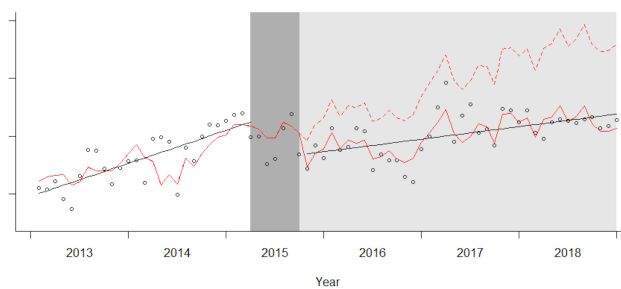
Rate of Ciprofloxacin Resistance Per 1000 Isolates



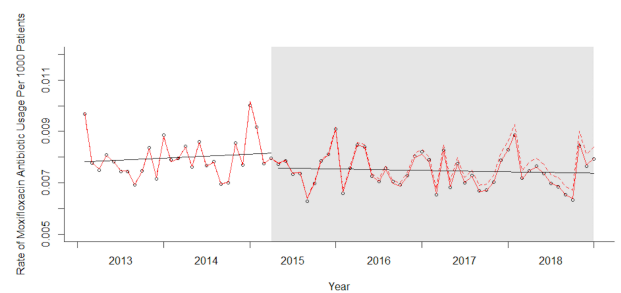
Co-amoxiclav



Rate of Co-amoxiclav Resistance Per 1000 Isolates



Moxifloxacin



Rate of Moxifloxacin Antibiotic Resistance Per 1000 Patients

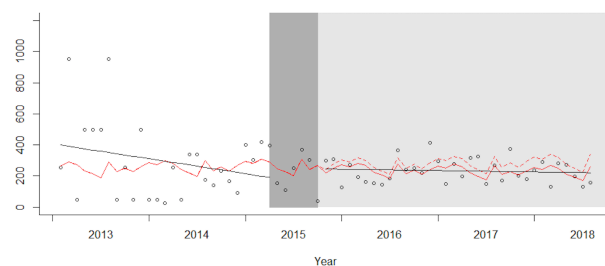




Figure 2. Rates of community antimicrobial exposure from 2013 to 2018 and GP practice level rates of resistance in *E. coli* community-onset *E. coli* bacteraemia isolates in England in relation to the QP antimicrobial stewardship intervention implemented in 2015, with counterfactual (dotted line) and linear regression segments (black lines)

GEE analysis results

The GEE model showed that the implementation of the QP had no impact on resistance to at least one of the five broad-spectrum antibiotics tested (IRR: 0.996; 95% CI: 0.986-1.003; p-value=0.207). After adjusting for prescribing, co-morbidities, age, deprivation index and geographical region, the effect of the QP did not change (IRR: 0.996; 95% CI: 0.987-1.005; p-value=0.410). The GEE model showed that in the long term, there was a sustained increase in the number of *E. coli* isolates resistant to at least one of the broad-spectrum antibiotics tested on implementation of the QP (IRR: 1.002; 95% CI: 1.000-1.003; p-value=0.047) (Table 3).

Table 3. Generalized Estimating Equation (GEE) models showing immediate and monthly effect of QP intervention on the number of community-onset *E. coli* bacteraemia isolates resistant to at least one of five antibiotics used for common infections

	IRR	Lower 95% CI	Upper 95% CI	p-value
Unadjusted model				
Immediate Effect After QP	0.9958	0.9862	1.0030	0.207
Long-term effect 39 months After QP	1.0012	0.9999	1.0030	0.080
Adjusted model¹				
Immediate Effect After QP	0.9962	0.9872	1.0053	0.410
Long-term effect 39 months After QP	1.0024	1.0000	1.0030	0.047

Abbreviations: IRR = Incidence Rate Ratio, CI = Confidence Interval.

¹Adjusted for prescribing for all 5 antibiotics per practice, the proportion of patients per GP practice with chronic obstructive pulmonary disorder (COPD), the proportion of patients per GP practice with chronic kidney disease (CKD), the proportion of patients in GP practice asthma, the proportion of patients in a GP practice with cancer, proportion of patients in a GP practice with diabetes, the proportion of patients in a GP practice aged between 0-14, the proportion of patients in a GP practice aged 65+, GP practice deprivation index, PHE region and season.

Sensitivity analyses

A sensitivity analysis was conducted looking at only those community-onset *E. coli* bacteraemia isolates that had a GP practice code recorded (n=138,576), compared with the dataset including imputed GP practice codes (descriptive analyses for practice-level and patient-level data for the fully observed dataset are presented in Supplementary Tables 6 and 7, respectively). The adjusted GEE model estimates on the effect of QP on resistance to these five antibiotics was similar for each dataset with the main model with imputed data showing a conservative estimate (IRR: 0.993 in the fully observed vs IRR: 0.997 in the imputed data). An additional sensitivity analysis was conducted looking at the effect of the QP in GP practices that saw the largest decreases in prescribing following its implementation. The adjusted GEE model estimates on the effect of QP on resistance to tested antibiotics was the same in the main dataset and the model with the interaction term (IRR: 0.993 in the model with the interaction term vs IRR: 0.997 in the imputed data). Finally, a sensitivity analysis was conducted using ITS analysis looking at the effect of the QP on ceftriaxone prescribing and resistance. The QP had no impact on ceftriaxone prescribing (IRR: 0.929 items per 1000 patients; 95% CI 0.817 to 1.057; p=0.955) or ceftriaxone resistance (IRR: 1.043 per 1000 isolates; 95% CI 0.905 to 1.201; p=0.562) (Supplementary Tables 3 to 5 and supplementary Figure 3).

DISCUSSION

This study provides information on trends in broad-spectrum prescribing and antibiotic resistance in *E. coli* bacteraemia isolates before and after the implementation of a national financial reward in 2015/16, the Quality Premium. The study findings demonstrate attainment of the QP objective of reducing the prescribing rate of co-amoxiclav and levofloxacin but not of ciprofloxacin, ofloxacin or levofloxacin. We observed a step-change in resistance to all antibiotics individually and in combination on implementation of the QP. However, the overall pattern was one of attenuation rather than a reversal of previously rising rates of antibiotic-resistant *E. coli* isolates, with the pre-intervention trend in rates of antibiotic resistance persisting in the long term.

This analysis has been strengthened by adjusting for antibiotic prescribing data in the analysis which similar studies have not controlled for.¹¹ Our previous work shows strong evidence of an association between antimicrobial prescribing and development of resistance.^{5,28} To advance our understanding of the impact of antimicrobial stewardship interventions on AMR and the resulting implications for policy and practice, evaluating both antimicrobial prescribing and AMR data is necessary. To our knowledge, this is the first study to conduct such an investigation using longitudinal data representative of the English primary care practices.

This study has some limitations. Firstly, antibiotic susceptibility testing (AST) reports made to the Second-Generation Surveillance System (SGSS) occur voluntarily which may lead to incomplete data collection. However, comparing bacteraemia rates from laboratories in the voluntary laboratory surveillance scheme with those reported to the mandatory surveillance scheme showed similar rates.³ Another possible limitation is the variation in definitions of clinical breakpoints. Most laboratories use EUCAST definitions of susceptibility to determine minimum inhibitory concentrations (MICs), which are considered more stringent²⁹, however, a small subset of laboratories use Clinical & Laboratory Standards Institute (CLSI) definitions. This may lead to discrepancies in interpreting AST results for specific bacteria, which could affect the overall results of this study. Yet even with the use of EUCAST breakpoints, it is not clear at any point in time what particular version laboratories might be using thus potentially overlooking breakpoint changes. Additionally, there are other factors that may explain the variability in isolate submission such as local policies around screening for serious infections such as sepsis (e.g. Commissioning for Quality and Innovation [CQUINs]).³⁰ Previous literature has cited increased detection of bacteraemia as an unintended consequence of policies that increase awareness of sepsis.³¹ Moreover, cephalosporins were not included in the main analysis. This is due to the majority of cephalosporins in primary care prescribed as cefalexin, a first-generation cephalosporin.^{12,32} *E. coli* bacteraemia isolate resistance to first-

generation cephalosporins is not commonly tested as a key drug/bug combination³³ and was thus unavailable in the reported data. Furthermore, second- and third-generation cephalosporins, are rarely prescribed in the community setting for managing common infections.¹² They are prescribed in specialist cases and are not an accurate reflection of community cephalosporin use.¹² Additionally, as this is an ecological study design with data aggregated at group-level, this may lead to bias due to ecological fallacy. Caution must be taken to avoid making inferences about antibiotic-resistant *E. coli* isolates from individual patients based on GP practice-level data. Finally, as this study originates in a high-income country, the generalisability of the study findings beyond other similar high-income settings are limited. Therefore, future work on addressing gap this is necessary.

Although the current study noted a reduction in prescribing following the implementation of a financial reward, which is consistent with previous studies,^{23,34} it has also been shown implementation of such interventions can have little effect after their implementation.³⁵ The reducing trend in total and individual prescribing demonstrated in the findings is consistent with previous studies.^{3,20,23} Notably, the 2019 English Surveillance Programme for Antimicrobial Usage and Resistance (ESPAUR) at PHE has reported a decrease in the total prescribing of antibiotics in primary care practices between April 2015 and March 2019. Decreases were also reported for co-amoxiclav and some quinolones.³ Our study found an increase in levofloxacin prescribing which is consistent with ESPAUR, which noted a consistent increase from 2014 to 2018.³ Other studies on the impact of the QP on antibiotic prescribing also showed a reducing trend in antibiotic prescribing in primary care.^{20,23}

The relationship between antibiotic prescribing and AMR has been established by a number of studies.⁴⁻⁷ Whilst there is evidence that reduction and restriction of antibiotic prescribing corresponds to a decrease in AMR in other similar high-income settings,^{36,37} previous research has noted persistent AMR despite decreasing prescribing.^{11,38-40} Several mechanisms may contribute to this. Firstly, whilst the use of penicillins, such as co-amoxiclav, has been shown to decrease in primary care, the use of penicillins in hospital inpatients has steadily increased.³ This may lead to increased *E. coli* bacteraemia resistance as it may promote the selection of antibiotic-resistant strains of organisms within the whole healthcare economy.⁵ Additionally, a study by Vihta *et al.* found that GP practices that prescribed more co-amoxiclav in the previous year were more likely to see more urinary tract infections caused by co-amoxiclav resistant *E. coli*.⁴¹ As *E. coli* bacteraemia are frequently known to be preceded by the underlying UTI, these UTIs may have then progressed to bacteraemia. Additionally, studies have noted that a decrease in prescribing may require many years, perhaps up to a decade, to reduce corresponding resistance which may suggest that effects of the QP intervention need more

time to manifest.³⁸ One study by Pouwels *et al.* noted that the use of specific antibiotics for *E. coli* UTIs, such as levofloxacin, is associated with resistance to other antibiotics used for other indications, such as ciprofloxacin, leading to co-selection of AMR *E. coli* isolates.⁴² Perhaps the most likely reason for the unhindered resistance despite falling antibiotic prescribing is the accumulation of mutations conferring resistance to antibiotics and acquired AMR genes within the bacterial populations.⁴³ Collignon *et al.* suggested that transmission of antibiotic-resistant genes was likely the most dominant contributor to AMR, implying that resistance might continue despite a restriction of prescribing.⁴³ This is of particular concern as the acquired AMR genes are usually present on mobile genetic elements (such as plasmids and transposons), that can be easily transmitted from one bacterial cell to another within the same species as well as between different bacterial species.⁴⁴ These mobile genetic elements can carry more than one AMR gene making bacterial isolates resistant to multiple antibiotics.⁴⁴ An example is the widely disseminated CTX-M enzyme which has become widespread globally and is responsible for most common antimicrobial resistance in *E. coli*, in the UK and the rest of Europe.⁴⁵ Furthermore, anthropogenic activities that rely heavily on antibiotic use such as animal husbandry and wastewater treatment become reservoirs which promote transmission of the aforementioned antimicrobial resistance genes.⁴⁵ These genes can then be transmitted to humans from the environment or through the food chain.⁴⁵

The present study has demonstrated that whilst the QP intervention has succeeded in reducing prescribing, resistance in *E. coli* causing bacteraemia, though attenuated following the implementation of the QP, remains on an upward trajectory. This study suggests that reducing prescribing, whilst effective in dampening resistance trends, may be insufficient as a standalone to curtail antimicrobial resistance in the primary care setting. AMR is a complex phenomenon which requires a collaborative effort across multiple sectors. We recommend surveillance of resistance genes for their early anticipation as there are irreversible genetic consequences of inappropriate antimicrobial use. The ability to identify the scale of genes that drive AMR and how the bacterial population evolve and adapt to changing pressures of antibiotics in use is important in the rational development of targeted measures, diagnostics and treatments to prevent and control bacteraemia caused by resistant *E. coli*.

Our findings suggest that focussing on reducing antibiotic use in primary care setting, a target for UK AMR strategy for many years, may be insufficient alone in countering resistance that has become established in the bacteraemia-causing *E. coli* population.

Contributors

SA contributed to the following: contributed to design and data analysis, data cleaning, conducting the analysis, interpreting results. PEA contributed to the following: designing the study, designing the data analysis plan, supervising the PhD student in conducting statistical analysis and in interpretation of results. CC contributed to the following: conceiving the study idea, designing and leading the study, designing the data analysis plan, supervising the PhD student in conducting statistical analysis and in interpretation of results. All authors contributed to the paper drafting and writing of the manuscript All authors commented on the revised manuscript, provided critical feedback and helped shape the overall manuscript.

Declaration of interests

APRW participated in Drug Safety Monitoring Board for Roche and has given lectures at MSD. All other authors declare no competing interests.

Data Sharing

The data that support the findings of this study are available from Public Health England. The data are compliant with the Data Protection Act (1998). Restrictions apply to the availability of these data. SA has an honorary contract with Public Health England for data access under CC's fellowship to access this data (grant reference: 2016-10-95). SA, PEA, CC, RH and BMP had access to and contributed to the verification and preparation of the data. The remaining co-authors did not access the data due to restrictions in the data sharing agreement for this study. Data are available with the permission of Public Health England with investigator support, after approval of a proposal, with a signed data access agreement.

Acknowledgements

The Department of Primary Care and Public Health is grateful for support from the NIHR Imperial Biomedical Research Centre funding scheme and the NIHR NW London Applied Research Collaboration. The views and opinions expressed here are those of the authors and do not necessarily reflect those of the NIHR or the Department of Health and Social Care. SA is funded as part of CC's NIHR Career Development Fellowship (grant reference: 2016-10-95). PEA is funded by the Economic and Social Research Council (ESRC) STEP-UP project through the Antimicrobial Resistance Cross Council Initiative supported by the seven research councils in partnership with other funders (grant reference: ES/P008232/1). The support of the ESRC is gratefully acknowledged. EJ is an Imperial College London Research Fellow jointly funded by Rosetrees Trust and The Stoneygate Trust 2017 (grant reference: M683). EJ also acknowledges funding from National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Imperial College London in partnership with Public Health England [HPRU-2012–10047]. CC is funded by a personal NIHR Career Development Fellowship (grant reference: 2016-10-95). APRW is part supported by the National Institute for Health Research University College

London Hospitals Biomedical Research Centre. The support of Dr Kate Honeyford at The Department of Primary Care and Public Health at Imperial College London is gratefully acknowledged.

REFERENCES

- 1 Neill JO'. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations
The Review on Antimicrobial Resistance Chaired. *HM Gov Wellcome Trust* 2014; : 1–20.
- 2 Public Health England. Annual epidemiological commentary: bacteraemia, MSSA
bacteraemia and C . difficile infections, up to and including financial year April 2018 to
March 2019. 2019; : 1–88.
- 3 Public Health England. English surveillance programme for antimicrobial utilisation and
resistance (ESPAUR). 2019; : 1–143.
- 4 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**: 1–25.
- 5 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**: 1120.
- 6 Report AJ. ECDC/EFSA/EMA second joint report on the integrated analysis of the
consumption of antimicrobial agents and occurrence of antimicrobial resistance in
bacteria from humans and food-producing animals: Joint Interagency Antimicrobial
Consumption and Resistan. *EFSA J* 2017; **15**. DOI:10.2903/j.efsa.2017.4872.
- 7 Wojkowska-Mach J, Godman B, Glassman A, *et al*. Antibiotic consumption and
antimicrobial resistance in Poland; Findings and implications 11 Medical and Health
Sciences 1117 Public Health and Health Services. *Antimicrob Resist Infect Control*
2018; **7**: 8–10.
- 8 Gray J, Oppenheim B, Mahida N. Preventing healthcare-associated Gram-negative
bloodstream infections. *J Hosp Infect* 2018; **98**: 225–7.
- 9 NHS England. Quality Premium : Guidance for 2017-19. *Dep Heal* 2018; : 1–32.
- 10 NHS England. About CCGs - NHS Clinical Commissioners. 2013; **53**: 1689–99.
- 11 Hernandez-Santiago V, Davey PG, Nathwani D, Marwick CA, Guthrie B. Changes in
resistance among coliform bacteraemia associated with a primary care antimicrobial
stewardship intervention: A population-based interrupted time series study. *PLoS Med*
2019; **16**: 1–19.
- 12 The National Institute for Health and Care Excellence (NICE) and Public Health
England (PHE). Summary of antimicrobial prescribing guidance - managing common
infections. 2019; : 1–23.
- 13 NHS Digital. Spine - NHS Digital. NHS. 2017. <https://digital.nhs.uk/spine> (accessed Oct
20, 2020).
- 14 EUCAST. EUCAST: New S, I and R definitions. <https://www.eucast.org/newsiandr/>.

696 15 Curtis HJ, Goldacre B. OpenPrescribing: Normalised data and software tool to research
697 trends in English NHS primary care prescribing 1998-2016. *BMJ Open* 2018; **8**: 1–10.

698 16 Nhsbsa.nhs.uk. Welcome | NHSBSA. <https://www.nhsbsa.nhs.uk/> (accessed July 27,
699 2020).

700 17 Salkind N. Encyclopedia of Research Design. 2455 Teller Road, Thousand Oaks
701 California 91320 United States: SAGE Publications, Inc., 2012
702 DOI:10.4135/9781412961288.

703 18 Deprivation M, Area LSO. The English Indices of Deprivation 2015 – Frequently Asked
704 Questions (FAQs). 2016; : 1–21.

705 19 Public Health England. Contacts: PHE regions and local centres. Gov.Uk. 2014.
706 <https://www.gov.uk/contacts-phe-regions-and-local-centres>.

707 20 Anyanwu PE, Pouwels K, Walker A, *et al*. Investigating the mechanism of impact and
708 differential effect of the Quality Premium scheme on antibiotic prescribing in England:
709 a longitudinal study. *BJGP Open* 2020; **4**: bjgpopen20X101052.

710 21 NHS Digital. Patients Registered at a GP Practice December 2019 - NHS Digital. 2019.
711 [https://digital.nhs.uk/data-and-information/publications/statistical/patients-registered-](https://digital.nhs.uk/data-and-information/publications/statistical/patients-registered-at-a-gp-practice/november-2019)
712 [at-a-gp-practice/november-2019](https://digital.nhs.uk/data-and-information/publications/statistical/patients-registered-at-a-gp-practice/november-2019)
713 [https://digital.nhs.uk/data-and-](https://digital.nhs.uk/data-and-information/publications/statistical/patients-registered-at-a-gp-practice/november-2019)
714 [information/publications/statistical/patients-registered-at-a-gp-practice/december-](https://digital.nhs.uk/data-and-information/publications/statistical/patients-registered-at-a-gp-practice/november-2019)
2019.

715 22 NHS Digital. Quality and Outcomes Framework, Achievement, prevalence and
716 exceptions data 2018-19 [PAS] data. Qual. Outcomes Fram. Achiev. Preval. Except.
717 2019. [https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-](https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2018-19-pas/main-findings)
718 [outcomes-framework-achievement-prevalence-and-exceptions-data/2018-19-](https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2018-19-pas/main-findings)
719 [pas/main-findings](https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2018-19-pas/main-findings).

720 23 Bou-Antoun S, Costelloe C, Honeyford K, *et al*. Age-related decline in antibiotic
721 prescribing for uncomplicated respiratory tract infections in primary care in England
722 following the introduction of a national financial incentive (the Quality Premium) for
723 health commissioners to reduce use of antibiotic. *J Antimicrob Chemother* 2018; **73**:
724 2883–92.

725 24 Ramsey EG, Royer J, Bookstaver PB, *et al*. Seasonal variation in antimicrobial
726 resistance rates of community-acquired Escherichia coli bloodstream isolates. *Int J*
727 *Antimicrob Agents* 2019; **54**: 1–7.

728 25 Deeny SR, van Kleef E, Bou-Antoun S, Hope RJ, Robotham J V. Seasonal changes in
729 the incidence of Escherichia coli bloodstream infection: Variation with region and place
730 of onset. *Clin Microbiol Infect* 2015; **21**: 924–9.

731 26 Ballinger GA. Using Generalized Estimating Equations for Longitudinal Data Analysis.
732 *Organ Res Methods* 2004; **7**: 127–50.

- 733 27 Huang Y, Carroll KC, Cosgrove SE, Tamma PD. Determining the optimal ceftriaxone
734 MIC for triggering extended-spectrum β -lactamase confirmatory testing. *J Clin Microbiol*
735 2014; **52**: 2228–30.
- 736 28 Bryce A, Hay AD, Lane IF, Thornton H V, Wootton M, Costelloe C. Global prevalence
737 of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli*
738 and association with routine use of antibiotics in primary care : systematic review and
739 meta-analysis. DOI:10.1136/bmj.i939.
- 740 29 Kassim A, Omuse G, Premji Z, Revathi G. Comparison of Clinical Laboratory Standards
741 Institute and European Committee on Antimicrobial Susceptibility Testing guidelines for
742 the interpretation of antibiotic susceptibility at a University teaching hospital in Nairobi,
743 Kenya: A cross-sectional stud. *Ann Clin Microbiol Antimicrob* 2016; **15**: 1–7.
- 744 30 NHS Improvement. Reducing the impact of serious infections CQUIN | NHS
745 Improvement. 2017; : 2–5.
- 746 31 Simmons MD, Daniel S, Temple M. Sepsis programme successes are responsible for
747 the increased detection of bacteraemia. *J Hosp Infect* 2019; **101**: 93–9.
- 748 32 Dolk FCK, Pouwels KB, Smith DRM, Robotham J V., Smieszek T. Antibiotics in primary
749 care in England: Which antibiotics are prescribed and for which conditions? *J*
750 *Antimicrob Chemother* 2018; **73**: ii2–10.
- 751 33 Wallace J. Advisory Committee on Antimicrobial Resistance and Healthcare Associated
752 Infection. *file:///Users/shirin/Desktop/9-cquin-guid-2015-16.pdf* 2013; : 1–25.
- 753 34 Balinskaite V, Johnson AP, Holmes A, Aylin P. The Impact of a National Antimicrobial
754 Stewardship Program on Antibiotic Prescribing in Primary Care: An Interrupted Time
755 Series Analysis. *Clin Infect Dis* 2018; **69**: 227–32.
- 756 35 MacBride-Stewart SP, Elton R, Walley T. Do quality incentives change prescribing
757 patterns in primary care? An observational study in Scotland. *Fam Pract* 2008; **25**: 27–
758 32.
- 759 36 Livermore DM, Hope R, Reynolds R, Blackburn R, Johnson AP, Woodford N. Declining
760 cephalosporin and fluoroquinolone non-susceptibility among bloodstream
761 Enterobacteriaceae from the UK: Links to prescribing change? *J Antimicrob Chemother*
762 2013; **68**: 2667–74.
- 763 37 Guillemot D, Varon E, Bernede C, *et al.* Reduction of Antibiotic Use in the Community
764 Reduces the Rate of Colonization with Penicillin G--Nonsusceptible *Streptococcus*
765 *pneumoniae*. *Clin Infect Dis* 2005; **41**: 930–8.
- 766 38 Enne VI, Livermore DM, Stephens P, Hall LMC. Persistence of sulphonamide
767 resistance in *Escherichia coli* in the UK despite national prescribing restriction. *Lancet*
768 2001; **357**: 1325–8.
- 769 39 Peñalva G, Fernández-Urrusuno R, Turmo JM, *et al.* Long-term impact of an

- educational antimicrobial stewardship programme in primary care on infections caused by extended-spectrum β -lactamase-producing *Escherichia coli* in the community: an interrupted time-series analysis. *Lancet Infect Dis* 2020; **20**: 199–207.
- 40 Sundqvist M, Geli P, Andersson DI, *et al.* Little evidence for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use. *J Antimicrob Chemother* 2009; **65**: 350–60.
- 41 Vihta KD, Stoesser N, Llewelyn MJ, *et al.* Trends over time in *Escherichia coli* bloodstream infections, urinary tract infections, and antibiotic susceptibilities in Oxfordshire, UK, 1998–2016: a study of electronic health records. *Lancet Infect Dis* 2018; **18**: 1138–49.
- 42 Pouwels KB, Muller-Pebody B, Smieszek T, Hopkins S, Robotham J V. Selection and co-selection of antibiotic resistances among *Escherichia coli* by antibiotic use in primary care: An ecological analysis. *PLoS One* 2019; **14**: 1–17.
- 43 Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planet Heal* 2018; **2**: e398–405.
- 44 Hughes D, Andersson DI. Evolutionary Trajectories to Antibiotic Resistance. *Annu Rev Microbiol* 2017; **71**: 579–96.
- 45 Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M β -lactamases: Temporal and geographical shifts in genotype. *J Antimicrob Chemother* 2017; **72**: 2145–55.