THE LANCET
Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Aliabadi S, Anyanwu P, Beech E, et al. Effect of antibiotic stewardship interventions in primary care on antimicrobial resistance of *Escherichia coli* bacteraemia in England (2013–18): a quasi-experimental, ecological, data linkage study. *Lancet Infect Dis* 2021; published online August 4. https://doi.org/10.1016/S1473-3099(21)00069-4.

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

Supplementary Material

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

	Mean number of items period before implementation of QP (Jan. 2013 to Mar. 2015, 27 months) (n = 6,882[1])				Mean number of items period after implementation of QP (Apr. 2015 to Dec. 2018, 45 months) (n = 6,882[1])			
	Mean	SD	Lower 95% CI	Upper 95% CI	Mean	SD	Lower 95% CI	Upper 95% CI
Ciprofloxacin	51·04	58·66	49·65	524·2	59·47	63·83	57·96	60·98
Co-Amoxiclav	364·50	333·32	356·62	372·38	517·25	436·23	506·94	527·56
Levofloxacin	3·78	12·83	3·47	4·08	8·21	25·21	76·2	8·81
Moxifloxacin	1·63	5·62	150	1·76	2·72	8·72	2·52	2·93
Ofloxacin	2·63	6·25	249	2·78	6·31	11·41	6·05	6·58
Total Antibiotics	423·58	364·19	4149·7	432·18	593·97	483·84	582·54	605·40

Abbreviations: CI = Confidence Interval, SD = standard deviation

[1] Number of GP practices included in study as the denominator

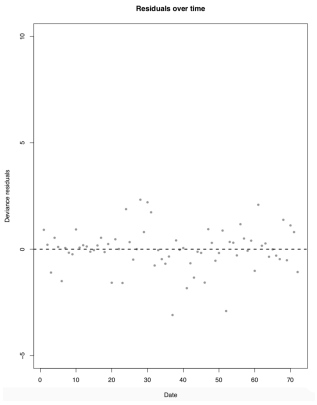
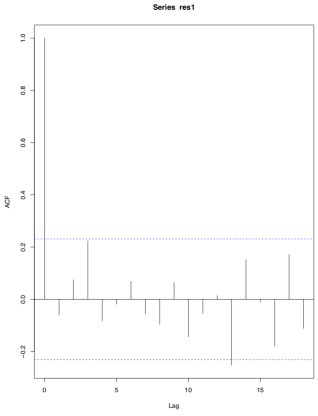
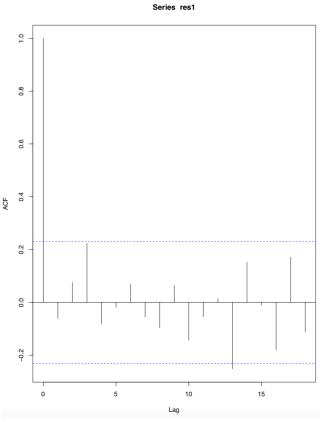
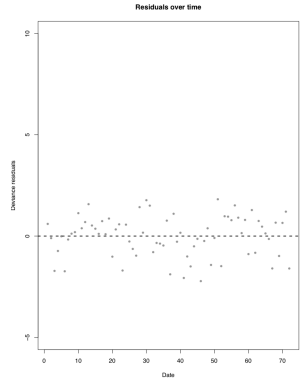
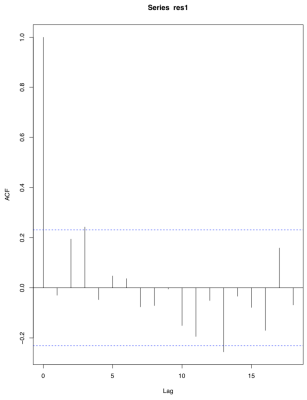
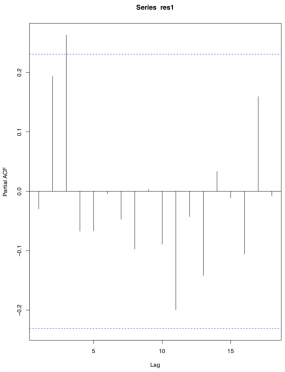
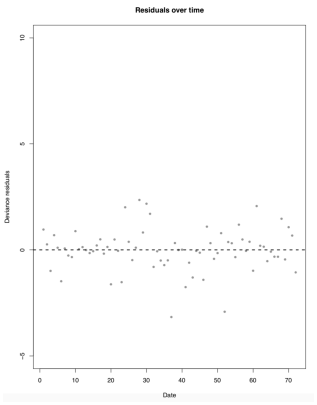
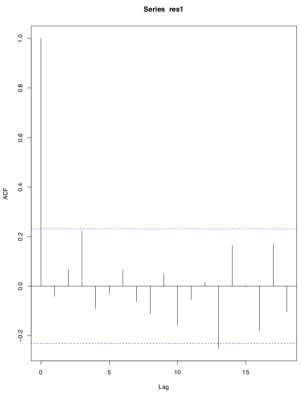
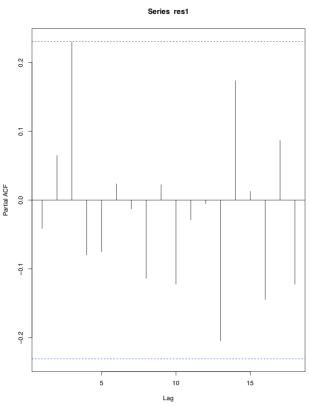
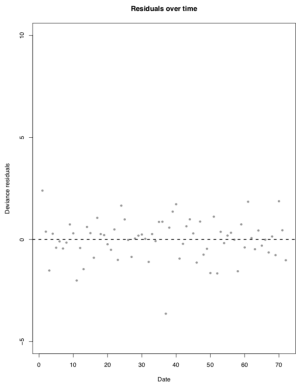
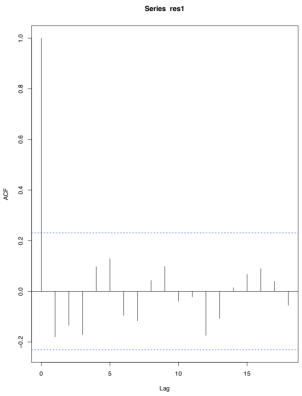
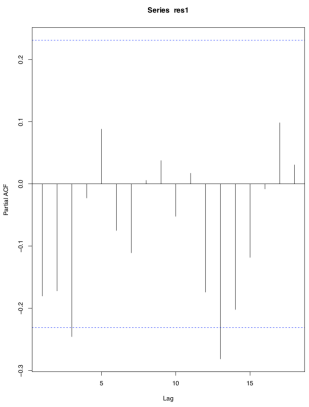
Supplementary Table 2. Characteristics of patients with community-onset *E. coli* bacteraemia between 2013-2018

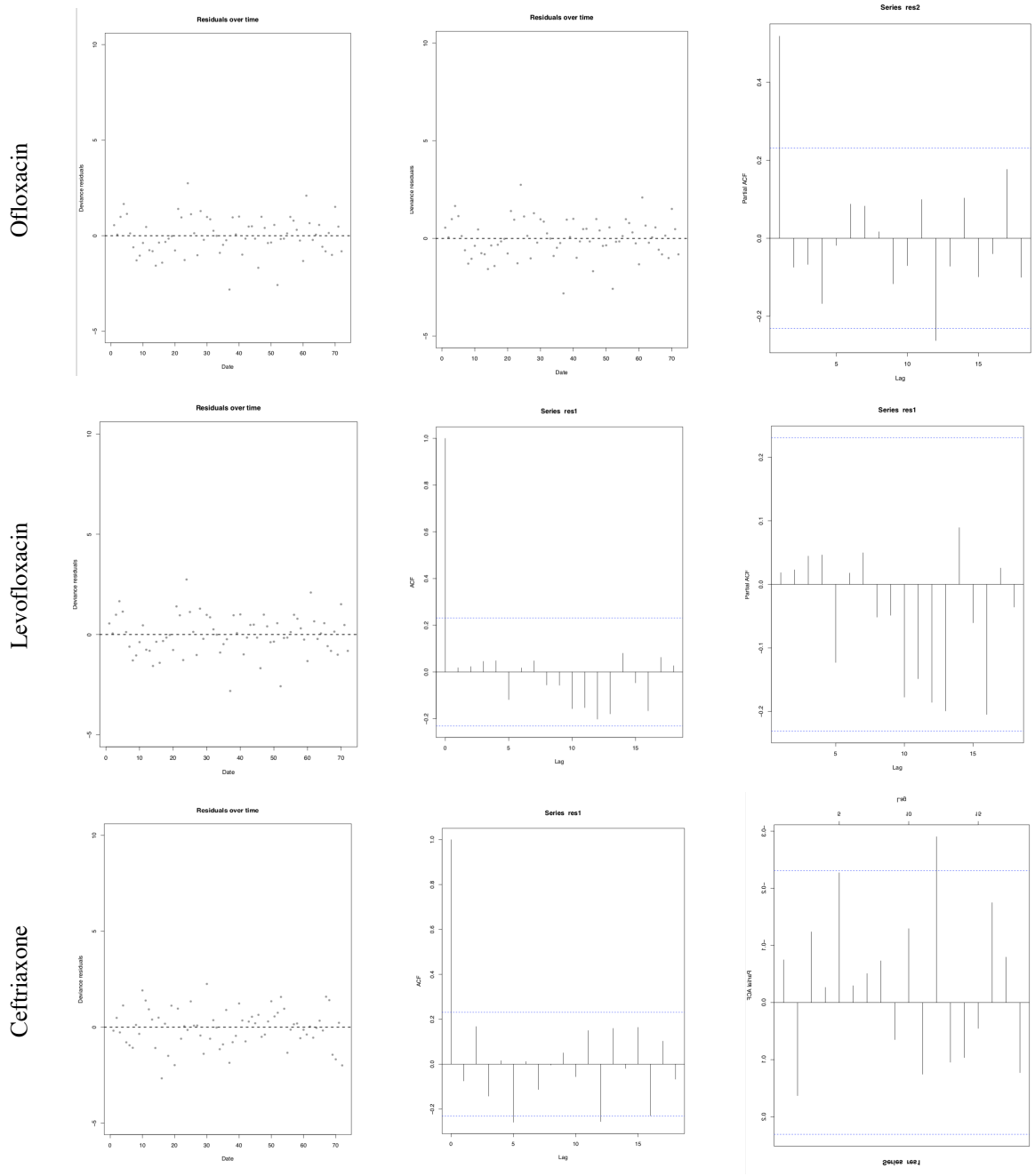
		Total (138,787)		Susceptible[3] isolates (84,078)		Resistant[3] isolates (54,709)	
		n	%	n	%	n	%
Gender[1]	**Male**	64,229	46·28	37,782	58·82	26,447	41·18
	Female	74,519	53·69	46,272	62·09	28,247	37·91
Patient age groups (in years)	**0 – 14**	2227	16·0	1584	71·13	643	28·87
	15 – 24	2647	19·1	1893	71·51	754	28·49
	25 – 64	33,248	23·96	20,974	63·08	12,274	36·92
	65+	100,665	72·53	59,627	59·23	41,038	40·77
Region	**London**	18,839	13·57	11,465	60·86	7374	39·14
	Southeast	21,606	155·7	13,202	61·10	8404	38·90
	Southwest	14,136	10·19	8716	61·66	5420	38·34
	West Midlands	16,031	11·55	10,584	66·02	5447	33·98
	East Midlands	12,144	8·75	6655	54·80	5489	45·20
	East of England	15,596	11·24	8226	52·74	7370	47·26
	Northeast	9068	6·53	6122	67·51	2946	32·49
	Yorkshire & Humber	12,757	9·19	8212	64·37	4545	35·63
	Northwest	18,610	13·41	10,896	58·55	7714	41·45
Tests against individual antibiotics[2]	**Ciprofloxacin**	119,095	85·81	98,528	82·73	20,567	17·27
	Co-Amoxiclav	119,140	85·84	71,968	60·41	47,172	39·59
	Levofloxacin	9386	6·76	7635	81·34	1751	18·66
	Moxifloxacin	2012	1·45	1392	69·18	620	30·82
	Ofloxacin	112	0·08	10	8·93	102	91·07

[1]Data were missing for 39 isolates

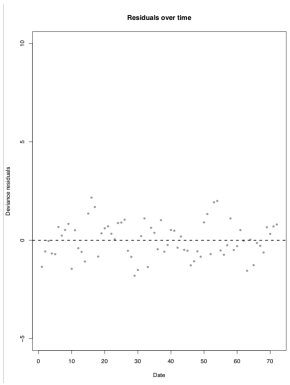
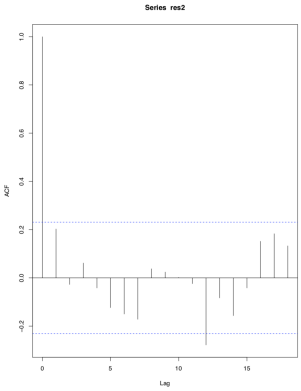
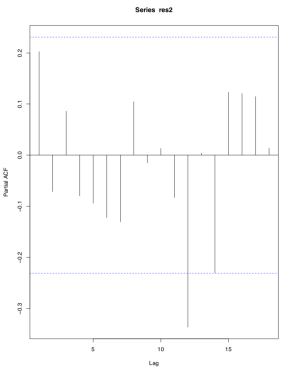
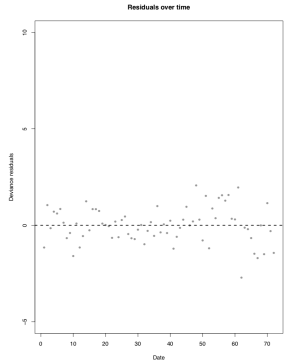
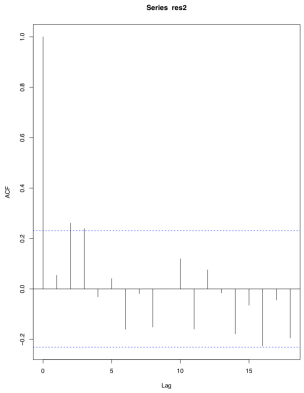
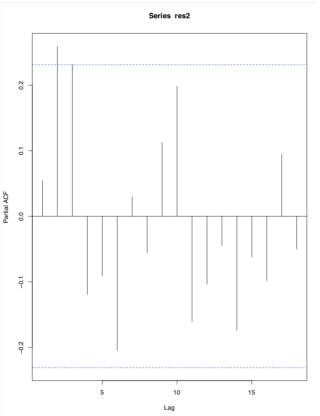
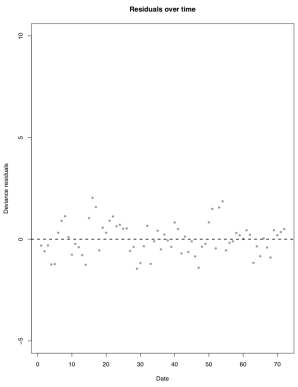
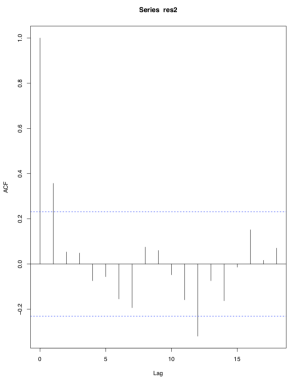
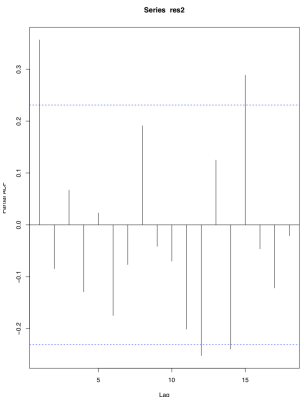
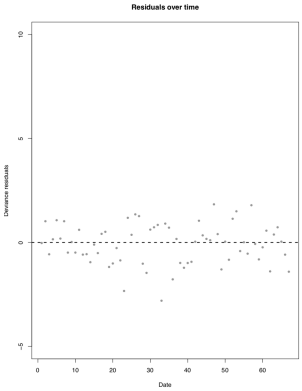
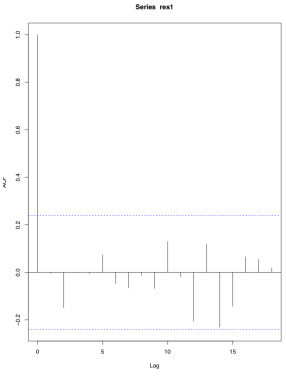
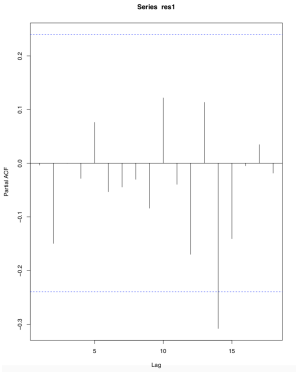
[2]Not all isolates were tested against each antibiotic during AST

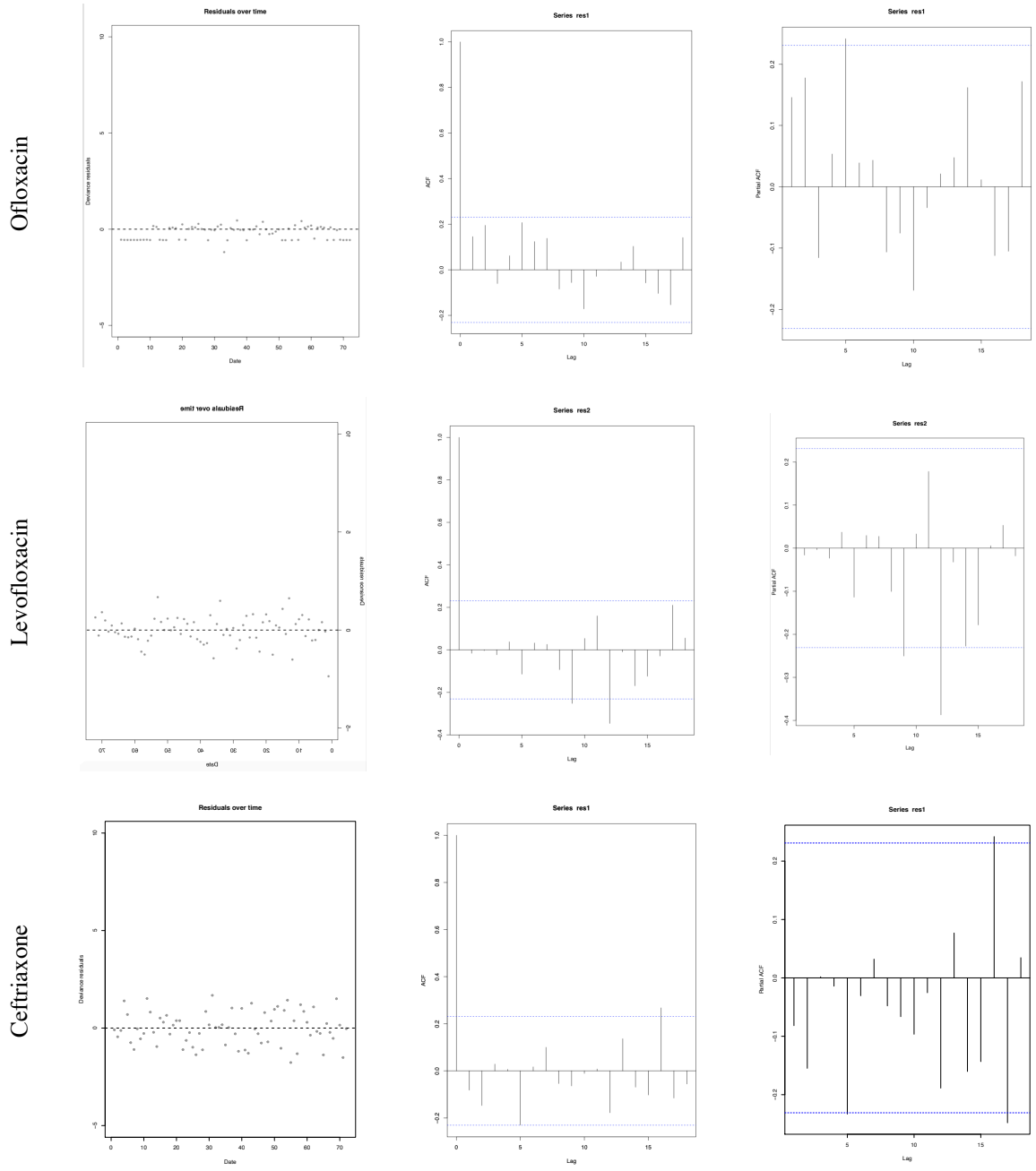
[3]Against at least one of five broad spectrum antibiotics tested

	Residual Plots	ACF Plots	PACF Plots
All Antibiotics			
Ciprofloxacin			
Co-amoxiclav			
Moxifloxacin			



Supplementary Figure 1. Residual, ACF and PACF plots for community antimicrobial exposure from 2013 to 2018 in England

	Residual Plots	ACF Plots	PACF Plots
All Antibiotics			
Ciprofloxacin			
Co-amoxiclav			
Moxifloxacin			



Supplementary Figure 2. Residual, ACF and PACF plots for GP practice level rates of resistance in *E. coli* community-onset bacteraemia isolates from 2013 to 2018 in England

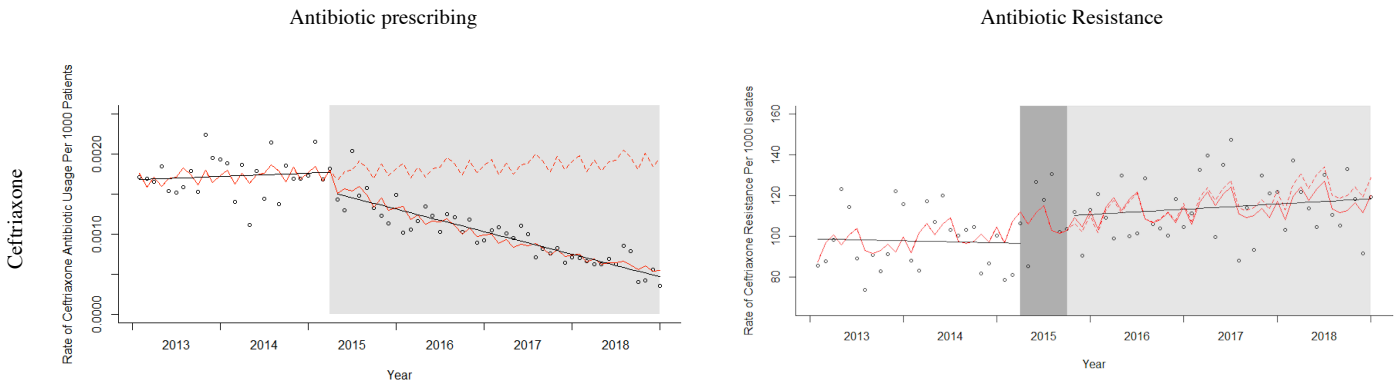
Supplementary Table 3. Interrupted time series analysis of changes in trends for antibiotic usage and antimicrobial resistance

	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]						
Ceftriaxone	0·000 (0·000 to 0·000)	1·002 (0·996 to 1·008)	0·929 (0·817 to 1·057)	0·974 (0·967 to 0·981)	0·001	-254·56
Antimicrobial Resistance[b]						
Ceftriaxone	0·094 (0·079 to 0·112)	1·004 (0·998 to 1·011)	1·043 (0·905 to 1·201)	0·998 (0·990 to 1·006)	8·78	6·83

Confidence intervals shown in brackets

[a] As a change in proportion of antibiotics prescribed per 1000 patients in GP practice

[b] As a change in proportion of resistant isolates per 1000 isolates submitted to Public Health England



Supplementary Figure 3. Rates of community ceftriaxone exposure from 2013 to 2018 and GP practice level rates of resistance in *E. coli* community-onset *E. coli* bacteraemia isolates tested against ceftriaxone in England in relation to the QP antimicrobial stewardship intervention implemented in 2015, with counterfactual (dotted line) and linear regression segments (black lines)

Supplementary Table 4. GP practice antibiotic prescribing for community-onset *E. coli* bacteraemia isolates with complete GP practice codes

	Antibiotics prescribed over entire study period (Jan. 2013 to Dec. 2018) (n = 6,866)				Antibiotics prescribed for 6-month period before implementation of QP (Oct. 2014 to Mar. 2015, 6 months) (n = 6,866)				Antibiotics prescribed for 6-month period after implementation of QP (Apr. 2015 to Sep. 2015, 6 months) (n = 6,866)			
	Mean	**SD**	**Lower 95% CI**	**Upper 95% CI**	**Mean**	**SD**	**Lower 95% CI**	**Upper 95% CI**	**Mean**	**SD**	**Lower 95% CI**	**Upper 95% CI**
Ceftriaxone	36·94	10·02	36·71	37·18	3·11	1·45	3·07	3·14	3·09	0·86	3·07	3·11

Abbreviations: CI = Confidence Interval, SD = standard deviation

Supplementary Table 5. Ceftriaxone resistance in *E. coli* causing community-onset *E. coli* bacteraemia between 2013-2018

		Total (138,576)		Susceptible[3] isolates (83,940)		Resistant[3] isolates (54,636)	
		n	%	n	%	n	%
Tests against individual antibiotics[1]	**Ceftriaxone**	31,570	22·8	27,776	87·98	3794	12·02

[1]Against at least one of five broad spectrum antibiotics tested

Supplementary Table 6. GP practice antibiotic prescribing for community-onset *E. coli* bacteraemia isolates for isolates with complete GP practice codes

	Antibiotics prescribed over entire study period (Jan. 2013 to Dec. 2018, 72 months) (n = 6,866[1])				Antibiotics prescribed for 6-month period before implementation of QP (Oct. 2013 to Mar. 2015) (n = 6,866[1])				Antibiotics prescribed for 6-month period after implementation of QP (Apr. 2015 to Sep. 2018) (n = 6,866[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	110·90	116·58	108·14	113·67	10·83	13·25	10·51	11·14	9·41	11·35	9·14	9·68
Co-Amoxiclav	883·93	738·04	866·44	901·42	86·74	81·31	84·81	88·66	73·77	67·80	72·16	75·37
Levofloxacin	12·04	36·80	11·17	12·91	0·99	3·76	0·90	1·08	0·86	3·34	0·78	0·94
Moxifloxacin	4·37	12·56	4·07	4·67	0·39	1,62	0·35	0·43	0·34	1·43	0·30	0·37
Ofloxacin	8·98	15·97	8·60	9·36	0·59	1·57	0·56	0·63	0·59	1·56	0·55	0·62
Total Antibiotics	1020·23	816·70	1000·88	10395·8	99·55	88·18	97·46	101·64	84·97	74·36	83·21	86·73

Abbreviations: CI = Confidence Interval, SD = standard deviation

[1] Number of GP practices included in study as the denominator

Supplementary Table 7. Characteristics of patients with *E. coli* community-onset *E. coli* bacteraemia between 2013-2018 for isolates with complete GP practice codes

		Total (138,576)		Susceptible[3] isolates (83,940)		Resistant[3] isolates (54,636)	
		n	%	n	%	n	%
Gender[1]	**Male**	64,129	46·30	37,712	58·81	26,412	41·19
	Female	74,408	5371	46,199	62·09	28,209	37·91
Patient age groups (in years)	**0 – 14**	2219	1·60	1577	71·07	642	28·93
	15 – 24	2641	1·90	1888	71·49	753	28·51
	25 – 64	33·185	23·95	20,933	63·08	12,252	36·92
	65+	100,531	72·55	58,542	58·23	40,989	40·77
Region	**London**	18,804	13·57	11,449	60·89	7355	39·11
	Southeast	21,590	15·58	13,191	61·10	8399	38·90
	Southwest	14,136	10·20	8716	61·66	5420	38·34
	West Midlands	16,013	11·56	10,567	65·99	5446	34·01
	East Midlands	12,057	8·70	6604	54·77	5453	45·23
	East of England	15,596	11·25	8226	52·74	7370	47·26
	Northeast	9068	6·54	6122	67·51	2946	32·49
	Yorkshire & Humber	12,748	9·20	8208	64·39	4540	35·61
	Northwest	18,564	13·40	10,857	58·48	7707	41·52
Tests against individual antibiotics[2]	**Ciprofloxacin**	118,943	85·83	98,407	82·73	20,536	17·27
	Co-Amoxiclav	118,988	85·86	71,873	60·40	47,115	39·60
	Levofloxacin	9385	6·77	7634	81·34	1751	18·66
	Moxifloxacin	2912	2·10	1392	47·80	620	21·29
	Ofloxacin	1612	1·16	10	0·62	102	6·33

[1]Data were missing for 39 isolates

[2]Not all isolates were tested against each antibiotic during AST

[3]Against at least one of five broad spectrum antibiotics tested

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

STROBE Statement

Checklist of items that should be included in reports of cross-sectional studies:

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 and 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 and 7
Bias	9	Describe any efforts to address potential sources of bias	7 and 10a
Study size	10	Explain how the study size was arrived at	6 and 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7 and 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	6 and 11
		(b) Indicate number of participants with missing data for each variable of interest	6, 8 and 11
Outcome data	15*	Report numbers of outcome events or summary measures	6 and 11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, 12, 15 and 16
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	11 and 16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4, 11 and 20