Effect of General Practice characteristics and antibiotic prescribing on *E. coli* antibiotic non-susceptibility in the West Midlands region of England – a four year ecological study

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Running Title: Association between antibiotic prescribing and non-susceptibility in the community.

Objectives: To assess the effect of general practice characteristics and antibiotic prescribing on the number of non-susceptible *E. coli* isolated from urine specimens submitted from community settings, we undertook an ecological study of the general practice population in the West Midlands.

Method: Descriptive analysis and multilevel modelling of temporal trends in antibiotic prescribing and non-susceptibility of *E.coli* urine isolates to a range of antibiotics prescribed in the community over a 4 year period.

Results: Nine of the 16 antibiotic prescribing / non-susceptibility combinations demonstrated a significant statistical linear correlation with non-susceptibility either for prescribing in the quarter or for prescribing within the previous 12 months. The magnitude of the effect varied, from a 0.3% increase in non-susceptibility to ampicillin/amoxicillin (when prescribing ampicillin/amoxicillin) to a 6.3% increase in non-susceptibility to nitrofurantoin (when prescribing nitrofurantoin) for an increase of 50 DDDs per 1000 practice population within a quarter (equivalent to approximately 10 courses of antibiotics). In 15 of the 16 models, single-handed general practices were shown to have a significant association with increased numbers of non-susceptible *E. coli* urine isolates (adjusted ORs 1.083 to1.606).
Increased prescribing of ampicillin / amoxicillin in winter periods was associated with increased non-susceptibility of *E. coli* isolated from urine specimens.

Conclusions: Small increases in antibiotic prescribing in individual general practices reduces the number of susceptible bacteria in the practice population. In order to

maintain the effectiveness of available treatment, antibiotic stewardship should be encouraged and supported within each practice.

Keywords

Antimicrobial resistance, antibiotic prescribing, urinary tract infection, general practice, community.

Introduction

Antimicrobial resistance (AMR) is a considerable threat to public health and the use of antibiotics has been cited as the single most important factor leading to antimicrobial resistance. [1] In 2014 in the UK, 74% of antibiotic prescribing occurred in general practice [2]. Antibiotic prescribing in the community is associated with the development of AMR: [3,4] however some community prescribers are sceptical that reduction in their antibiotic prescribing will reduce the levels of AMR in their practice population. [5] Other factors such as the practice location, length of appointment, [6] social deprivation [7] and single-handed practices [8] have been shown to be associated with increased antibiotic prescribing in the UK.

The Chief Medical Officer (CMO) for England in her 2011 annual report promoted the use of antibiotic stewardship as a measure to control the development and spread of AMR; [9] however a study in 2014 reported that Public Health England (PHE) clinical prescribing guidance has not reduced prescribing in the community. [10]

Urinary tract infections (UTI), and in particular those caused by *Escherichia coli*, were the focus of this study because UTIs are one of the most common conditions diagnosed in community settings in Europe and are an important clinical indication of prescribing in primary care, [11] with *E. coli* being the commonest cause of UTIs in both primary and secondary care. [12]

A systematic review of studies reporting on the association between antibiotic prescribing and resistance reported that the inability to measure the time between prescribing and detection of resistance, control for practice / population

characteristics or examine co-selection (use of one antibiotic leading to resistance in another antibiotic) has been a limiting factor when interpreting results. [3]

To address some of the gaps in previous studies, we undertook an ecological study to examine the relationship between prescribing antibiotics commonly used in general practice and non-susceptibility of *E. coli* isolates from urine samples taken in general practices in the West Midlands region of England over a 4 year period.

Methods

Setting / Population

In 2012 there were 950 general practices with 3635 general practitioners serving a population of 5.8 million registered patients in the West Midlands Region. [13] During 2010-2014, there were 15 diagnostic microbiology laboratories serving both community-based healthcare centres and hospitals.

Data sources

Antibiotic prescribing data on items dispensed in each general practice during the period 2010-2014 was obtained from NHS Digital (previously known as the Health and Social Care Information Centre). [14] Antibiotic prescribing data is expressed as defined daily doses (DDD) per 1000 general practice population.

Data on antibiotic non-susceptibility for *E. coli* isolates from urine specimens submitted from general practices was obtained from the Public Health England (PHE) Second Generation Surveillance System (SGSS), previously known as the

AmSurv system. [15] To detect emerging non-susceptibility, we de-duplicated the dataset by removing only duplicate *E. coli* reports from each patient having exactly matching antibiotic susceptibility results within the same year. Nine of the15 laboratories were reporting data regularly to SGSS/AmSurv at the start of our study period in 2010, and complete coverage of all 15 laboratories was achieved in 2012. Non-susceptibility to an antibiotic was defined as test results with a 'resistant' (R) or 'intermediate' (I) designation. The antibiotics included in the study are detailed in Table 1.

Data on general practice characteristics was obtained from the National Health Service (NHS) Business Services Authority (http://www.nhsbsa.nhs.uk/). This included data on the total practice population, proportion of the practice population <15 years old and ≥ 65 years, and ratio of females to males in the practice population. The number of general practitioners (GPs) within each practice was obtained from NHS Digital, with single-handed practices defined as those practices with only one registered GP. [16]

We measured social-economic deprivation using data from the English Index of Multiple Deprivation 2010. [17] A deprivation index was assigned to each general practice based on the deprivation index assigned to the Local Authority (English administrative area) in which the practice was located.

The general practices were categorised as 'urban' or 'rural' based on whether the majority of the population in the Local Authority in which the practice is situated live in a rural or urban setting. [18]

Descriptive analysis

Seasons were defined as spring (March to May), summer (June to August), autumn (September to November), and winter (December to February). We calculated seasonal total DDD prescribing quantities and DDDs /1000 practice population for the period March 2010 to February 2014. These were compared with non-susceptibility proportions for *E. coli* urinary isolates against the 6 antibiotics selected for analysis in order to describe prescribing and non-susceptibility trends during the study period.

Statistical analysis

Sixteen separate datasets were created. Each dataset consisted of data on all reported *E .coli* isolates non-susceptible to one of the 6 selected antibiotics by practice, alongside matching practice prescribing data for the same antibiotic or another commonly prescribed antibiotic that may select non-susceptibility (Table 1). Antibiotic combinations were selected based on biological plausibility of an exposure/non-susceptibility relationship and to enable comparisons with other international studies.[3] For each combination, seasonal quarterly trends in non-susceptibility of *E. coli* isolates for each general practice from 01/03/2010 to 28/02/2014 were compared to trends in antibiotic prescribing data in the same quarter and previous quarters (up to four lagged quarters).

National community prescribing guidance recommends course lengths of between 3 – 10 days depending on the antibiotic and the clinical presentation. [19] We therefore set a prescribing unit within the statistical models of 50 DDDs, which represents approximately 10 prescriptions, taking an average of 5 days for each course.

General practice characteristics were included in the statistical models as potential explanatory variables (Table 2).

Multilevel mixed-effects generalised linear models, using a binomial distribution for the outcome, were developed to examine the relationship between antibiotic use and *E.coli* non-susceptibility. Each statistical model (one for each prescribing / non-susceptibility combination) consisted of the number of *E. coli* isolates non-susceptible by general practice as the outcome variable, number tested as the denominator, as well as the various explanatory variables, including antibiotic prescribing in the current and lagged prescribing quarters described above, which formed the fixed-effect portion of the models. A composite group variable was created using general practice and Local Authority area to form a 2nd level random intercept to allow modelling of variability between these hierarchical populations as random effects. Likelihood ratio testing was used to determine significance and a *P* value of ≤0.05 was considered statistically significant. Adjusted odd ratios were used as a measure of association.

Cubic functions of all continuous variables explanatory variables were constructed and then subsequently tested for linearity via a stepwise iterative process. Significant non-linear variables were retained and tested to determine if they were still significant when inserted into the model together. When satisfied that any remaining non-linear terms were still significant when tested together in the model, the significance of the linear covariates were tested. All lagged prescribing quarters were included in each of the statistical models; however as prescribing data prior to 2010 was not available, to increase the number of complete observations the DDD/1000 practice population variable with the greatest lag was removed if it was

found to be not statistically significant, and was not a substantial confounder (i.e. its removal did not lead to a >10% change in the odds ratios of the linear variables). The model building process was then repeated with the increased number of comparable observations.

All other explanatory variables were retained in a linear or non-linear form, depending on which form was found to best fit the data within each model (see supplementary data file).

All statistical analyses were performed using STATA v13 (StataCorp, USA).

Results

During the study period there were 313,085 *E. coli* reports from urine specimens submitted by West Midland GPs. These represented 247,971 de-duplicated laboratory reports of *E. coli*, from 181,764 patients, submitted by 911 of 948 (96%) general practices prescribing antibiotics in the West Midlands.

The proportion of *E.coli* isolates tested against the selected antibiotics and the proportion reported as non-susceptible during the study period are shown in Table 3. Data from all 948 general practices that prescribed antibiotics in the West Midlands during the study period were included. The quantity of antibiotic prescribing varied widely across general practices. In 2013, the 5th and 95th percentile for total antibiotics prescribed by individual West Midland general practices was 4431 DDD/1000 population and10076 DDD/1000 population. In 2013, a total of 45 million antibiotic DDDs were prescribed in the West Midlands. Amongst the antibiotics

included in the study, ampicillin / amoxicillin was the most commonly prescribed in 2013 with13.6 million DDDs, followed by co-amoxiclav with 2.9 million DDDs and trimethoprim 2.8 million DDDs.

Fifteen percent (141/948) of general practices were single-handed (Table 2), and 82% (116/141) of these were designated as being in rural locations. When comparing single-handed GPs as a group, the prescribing rate was consistently higher throughout the study period than the group consisting of non-single handed GP practices (Figure 1).

Increased non-susceptibility to ampicillin/amoxicillin was observed in *E. coli* urine isolates in the winter periods which mirrored observed winter peaks in prescribing of ampicillin/amoxicillin (Figure 2). Seasonal changes in antibiotic prescribing and non-susceptibility was not observed for other antibiotics included in the study.

Nine of the sixteen multi-level mixed effects statistical models showed a statistically significant linear relationship between *E.coli* non-susceptibility and the prescription of defined antibiotics during the same seasonal quarter or prescribing within the previous 12 months. Three of the remaining models showed statistically significant non-linear relationships for some of the seasonal quarters, and 4 models had no statistical associations between the prescribed antibiotic and non-susceptibility (please see supplementary data for complete modelling results).

Ampicillin/amoxicillin was the only antibiotic for which the odds of increased *E.coli* non-susceptibility was associated with an increase in prescribing within the same

quarter, when prescribing ampicillin/amoxicillin and co-amoxiclav (OR 1.003, 95% CI 1.001 - 1.006 and OR 1.006, 95% CI 1.002 - 1.009 respectively).

There was also an association between prescribing in previous quarters, and increased non-susceptibility of *E. coli* to co-amoxiclav (when prescribing ampicillin/amoxicillin), ciprofloxacin (when prescribing fluoroquinolones), nitrofurantoin (when prescribing cephalexin and nitrofurantoin) and trimethoprim (when prescribing trimethoprim) (Table 4).

The magnitude of the statistical associations varied. In model 2, for every increase of 50DDD per 1000 population of ampicillin within the same quarter we found an increase in the odds of ampicillin/amoxicillin non-susceptibility of 0.3% (95% CI 0.2% - 0.6%, p= 0.001). In model 14, for every increase of 50DDD per 1000 population of nitrofurantoin within the previous quarter we found an increase in the odds of nitrofurantoin non-susceptibility of 6.3% (95% CI 1.3% -11.5%, p= 0.013).

There was a significant negative association in the same quarter with non-susceptibility to: co-amoxiclav when prescribing ampicillin/amoxicillin, ciprofloxacin when prescribing co-amoxiclav, trimethoprim when prescribing trimethoprim and in the same quarter and in the previous 12 months for nitrofurantoin when prescribing nitrofurantoin (Table 4), indicating increased prescribing in those periods are associated with lower numbers of non-susceptible *E. coli*.

A statistically significant positive association was found between *E. coli* non-susceptibility and single-handed practices in all 16 prescribing / non-susceptibility statistical models (Table 5), with a single-handed practice associated with increased numbers of non-susceptible *E. coli* urine isolates (adjusted ORs 1.083 -1.657).

Discussion

Our study showed that small increases in antibiotic prescribing by general practices in the West Midlands for a range of antibiotics increased the odds that *E. coli* UTI isolates from the practice population would be non-susceptible to one or more antibiotics.

Although an ecological study across a large regional population, our findings of an association between ampicillin/amoxicillin non-susceptibility in *E .coli* and prescribing levels during the same time period are similar to those from patient-level studies in England in 2005 and Wales in 2007. [20,21]. The Welsh study also supports our findings of no statistical association between ampicillin/amoxicillin non-susceptibility and prescribing of ampicillin/amoxicillin twelve months prior to the susceptibility tests. [21]

A 2007 study of a large portion of the general practice population in Wales found a statistically significant decrease in ampicillin resistance of 1.03% for every decrease of 50 amoxicillin items dispensed per 1000 patients per annum and a decrease in trimethoprim resistance of 1.08% for every decrease of 20 trimethoprim items dispensed per 1000 patients per annum, [22] which supports our findings, only in the opposite direction as we measured the effect on non-susceptibility by small increases in antibiotic prescribing.

The immediate effect described of increased *E. coli* non-susceptibility to ampicillin/amoxicillin with increased prescribing of beta-lactam antibiotics (Models 1 and 2) may be due to the selection and rapid multiplication of TEM beta-lactamase

producing strains [23] (Table 4). It is therefore plausible that the selection of these strains would have a negative association with co-amoxiclav, as observed in Model 4, as this antibiotic remains active against common TEM beta-lactamases. The successful *E. coli* urinary pathogenic clonal group ST131 is associated with combined non-susceptibility to beta-lactam antibiotics and fluoroquinolones, [24] and therefore the successful action of co-amoxiclav against these strains may also reduce the population non-susceptible to ciprofloxacin, as observed in Model 5. The negative association with non-susceptibility to co-amoxiclav (prescribing ampicillin/amoxicillin) and trimethoprim (prescribing trimethoprim) in the immediate quarter is reversed in previous prescribing quarters with a positive association, suggesting sufficient time had elapsed for a previously susceptible population to acquire resistance.

Nitrofurantoin remains active against multi-drug resistant (MDR) *E.coli*, which may explain the negative association with non-susceptibility and increased prescribing of nitrofurantoin in the same quarter. Non-susceptibility to nitrofurantoin is conferred by mutation, and we observe increased odds of non-susceptibility when prescribing nitrofurantoin in the previous quarter. A study from Sweden in 2013 [25] suggests that the establishment of *E. coli* clones non-susceptible to nitrofurantoin is unlikely due to the severe fitness cost imposed by the required mutation. This may explain the negative association we observe in prescribing nitrofurantoin 12 months previously (Model 14).

To our knowledge, this is the first study to show that single-handed practices are associated with higher levels of antibiotic non-susceptibility. A systematic review measuring the effectiveness of single- handed practices suggested that the observed

higher general prescribing rates by these practices may be due to higher workloads, shorter appointment times and the lack of opportunity to discuss prescribing protocols with colleagues. [26] Although we report that 15% of practices in the West Midlands were single-handed, there has been a move towards group practices in England; however in many parts of Europe single-handed practices still predominate. [26]

We report an observed temporal relationship between prescribing ampicillin/amoxicillin and non-susceptibility to this antibiotic in *E. coli* urine isolates, with peaks in the winter months (Figure 2). In a study in the USA in 2012 similar seasonal relationships were demonstrated for a number of combinations of prescribed antibiotics and resistance, including a correlation of prescribing aminopenicillins (lagged by 1 month) and resistance in all *E. coli* isolates. [27] Ampicillin/amoxicillin prescribing represented 30% of the total quantity of antibiotics prescribed in the West Midlands in 2013. In the UK, amoxicillin is not first-line treatment for UTI, but it is first-line treatment for many community respiratory infections. [19] It is therefore plausible that the winter peaks in prescribing for respiratory conditions is selecting non-susceptibility in urine isolates. A recent UK study found that most general practices over-prescribe for respiratory conditions. [28] A randomised controlled trial in 2005 showed use of narrow spectrum antibiotics rather than amoxicillin resulted in comparable clinical outcomes among hospitalised patients with community-acquired pneumonia. [29] Our findings suggest this approach may also result in reduced numbers of non-susceptible *E. coli* in the population.

This is a retrospective ecological study and therefore is not able to draw inferences about individual risk of antimicrobial resistance. Significant statistical associations in these types of studies should be interpreted as only suggestive as they do not necessarily imply cause –effect relationships. Whilst this is a limitation it was noted in a large review in 2013 of individual patient and ecological studies that antibiotic pressure at population level maybe more important in determining risk of harbouring resistant bacteria in the community. [3]

DDDs were chosen as the metric for antibiotic prescribing as they are the most commonly applied unit of measurement and are recognised internationally as a bench-marking measure. It also allowed comparison with international studies comparing prescribing with antibiotic resistance. However it is recognised that DDDs do not always accurately reflect prescribing for children or persons with renal impairment.

Multilevel modelling is a strength of this study as it allows random effects in the population to be taken into account whilst adjusting for a number of potential predictor or confounding variables. Following a review of the literature we found only a limited number of studies included practice characteristics and of these comparable interactions between these variables with either not found, [20] or were not reported. [6] A systematic approach of testing potential interactions was considered for our study; however this would have added over 30 pairwise combinations of variables. Therefore to ensure manageability and aide interpretation we chose to focus on the main effects of the various variables included in this study. We intend to examine potential interactions between practice characteristics in a future study.

Seven of the 16 statistical drug/bug combination models developed did not show linear relationships between the prescribed antibiotic and non-susceptibility in *E. coli* urine isolates. Three of these models, however, did show significant non-linear associations between prescribing and non-susceptibility for some of the seasonal quarters, and this will also form part of the new study.

Given the plausibility of bacteria carrying resistance genes to multiple antibiotics, there will be interdependence between some of the antibiotic combinations when measured against the same antibiotic non-susceptibility results. Therefore with the large amount of testing captured in this study we would expect to encounter a number of type one errors for particular antibiotic combinations. A more stringent significance test was considered; however this was not implemented due to the possibility of increasing the number of false negative associations.

The antibiotic non-susceptibility data were extracted from routine laboratory reporting and therefore is subject to specimen selection bias as it is likely that urine samples sent for microbiological examination are from patients with treatment failures or those that have complicated and/or severe infections. [12] Notwithstanding this, it is encouraging that a study in Ireland in 2012 of urines taken from all adult patients suspected of having a UTI attending 22 practices found similar antibiotic susceptibility proportions. [30] We also found little variation in susceptibility proportions, reported in Table 3, between the de-duplicated data and all *E. coli* reports, providing confidence that this process was not inflating non-susceptibility in our modelling dataset.

As we reported previously, there is variation in antibiotic susceptibility testing methods in West Midland laboratories[12] and laboratories varied slightly in the

antibiotics selected for first-line testing (Table 3). During this period 13 of the 15 laboratories applied the most recent BSAC or EUCAST MIC breakpoint standards and all laboratories participated in monthly internationally accredited external quality control assessment of susceptibility testing methods [31].

The West Midlands was the first region of England to implement routine AMR surveillance reporting and achieve complete reporting from local laboratories. [15] Not all laboratories were reporting at the beginning of the study in 2010, however a comparison of the overall antibiotic susceptibility data from the 9 laboratories reporting throughout the study period showed little variation with susceptibility data from all 15 laboratories. Multilevel mixed effects generalised linear models do allow for missing data; however, although the missing laboratories consisted of a cross-section of laboratory sizes situated in both urban and rural localities, we accept that the missing AMR data in the first period of the study may bias the data.

This large AMR dataset, for the first time, provides an opportunity to analyse the association between prescribing and resistance in a large English regional population. We are beginning to receive patient level prescribing data from the community and therefore we now have the opportunity to build on this study by further exploring the relationship between prescribing and antibiotic resistance.

In summary our statistical models suggest that small increases in antibiotic prescribing within a general practice increases the number of non-susceptible bacteria isolated in urine samples within the practice population. We have shown that the large volumes of antibiotics likely to have been used in the treatment of respiratory conditions in winter months, appears to have an immediate short-term

effect of increased antibiotic non-susceptibility in bacteria causing unrelated infections. Prudent prescribing, in line with Royal College of General Practitioners guidance (http://www.rcgp.org.uk/clinical-and-research/toolkits/target-antibiotics-toolkit.aspx) is required by individual general practices, particularly in winter periods, to maintain a population of susceptible bacteria in their local population, thereby preserving the effectiveness of available antibiotics. We have also shown that a single-handed GP practices may require additional antibiotic stewardship support and guidance.

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Transparency declaration

PMH has received honoraria for developing and delivering educational presentations for Eumedica, Pfizer, Merck, Novartis, MagusCommunications, Wyeth, Bio Merieux, Becton-Dickinson; funded research from Pfizer, Eumedica; Consultancy for Pfizer, Novartis, Novacta, Novolytics, Merck, Wyeth, Optimer. He is a director of ModusMedica a medical education company.

All other authors have no competing interests.

Ethics

PHE has approval under Section 60 of the Health and Social Care Act 2001 (now subsumed into the National Information Governance Board for Health and Social Care with Section 60, now Section 251 of the NHS Act 2006) to process confidential patient information for public health surveillance (see http://www.legislation.hmso.gov.uk/si/si2002-20021438.htm). However, the AMR surveillance data extracted for this study did not include patient identifiers and general practice identifiers were anonymised when creating the models.

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Table 1: Antibiotic combinations evaluated to measure commonly associated resistance mechanisms found in E. coli and enable comparison with international studies

***Escherichia coli* non-susceptibility**	**Prescribed antibiotic**	**Statistical model no.**
Ampicillin / amoxicillin	ampicillin/amoxicillin	2
	co-amoxiclav	1
	fluoroquinolones	3
Cephalexin	cephalosporins	10
	fluoroquinolones	11
	trimethoprim	16
	nitrofurantoin	12
Co-amoxiclav	co-amoxiclav	9
	ampicillin/amoxicillin	4
Ciprofloxacin	ampicillin/amoxicillin	6
	fluoroquinolones	8
	co-amoxiclav	5
	Cephalexin	7
Trimethoprim	trimethoprim	15
Nitrofurantoin	nitrofurantoin	14
	Cephalexin	13

Table 2. Explanatory variables included in the multi-level mixed effects statistical model

General Practice characteristics	**West Midlands mean or % (if applicable)**
General practice list size	6252
Registered patient gender ratio (female/male)	0.98
Proportion of registered patients aged under age 15 years	18.21%
Proportion of registered patients aged 65 years and over	16.15%
Practices with one registered GP	15%
Number of registered patients per GP	1700.31
Location deprivation index (IMD2010)	28.14
Rural practice location	27%
Time variables	
Seasonal quarter (March-May, June-August, September-November, December - February)	
Time variable for study period	

Table 3. Percentage of antibiotic tests and non-susceptibility, March 2010 – November 2013.

Antibiotic	***E. coli* tested (%)**	***E. coli* non-susceptible (%)**
Ciprofloxacin	77.2	11.8
Co-amoxiclav	88	18.2
Cephalexin	83.4	6.9
Ampicillin/Amoxicillin	85.1	52.1
Nitrofurantoin	99.8	2.7
Trimethoprim	99.9	34.8

Figure 1 Seasonal trends in total antibiotic prescribing rates by practices with a single general practitioner (GP) and those with multiple GPs West Midlands, March 2010 – November 2013.

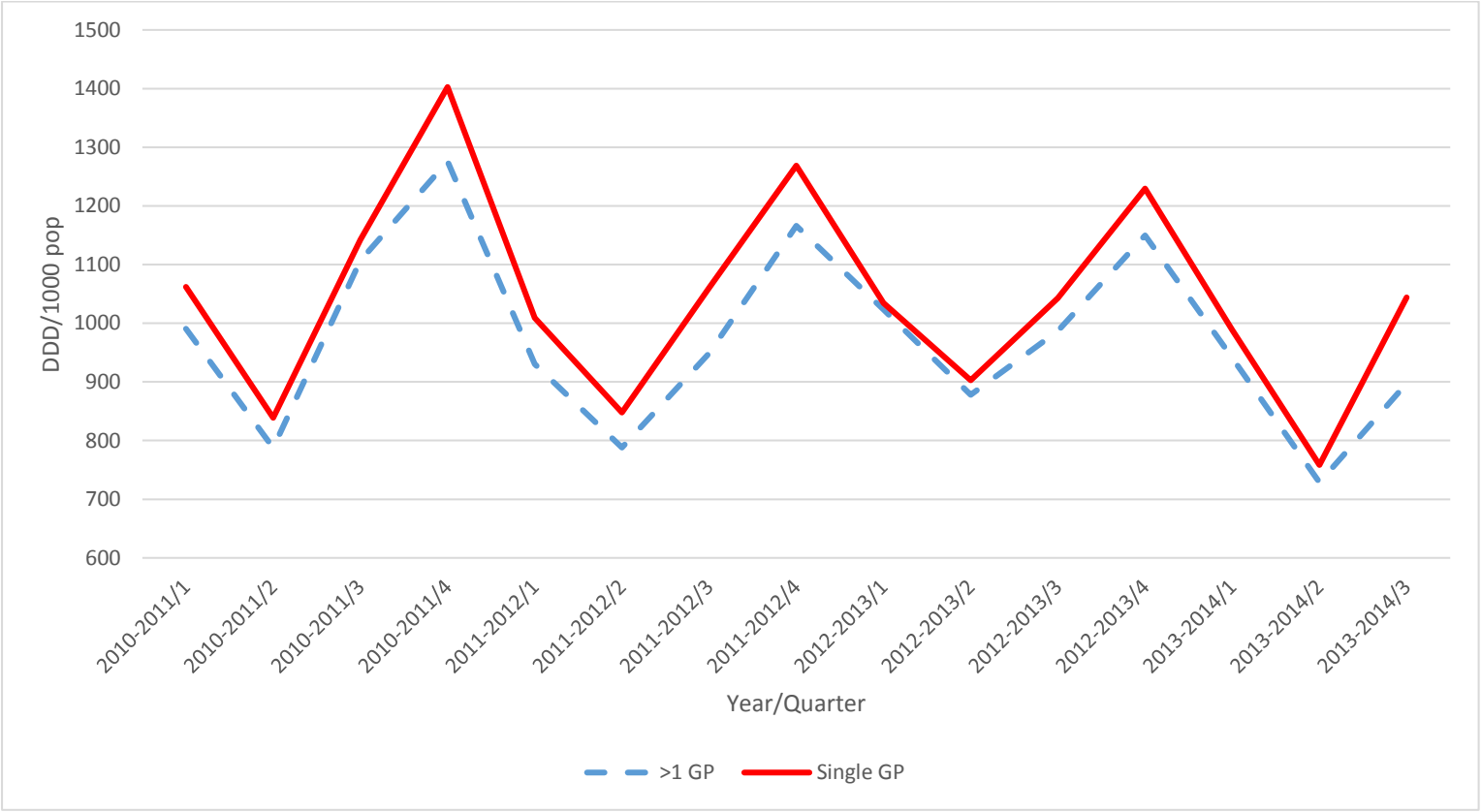

Figure 2. Ampicillin/amoxicillin prescribing and non-susceptibility of *E. coli* urine isolates, West Midlands 2010-2013

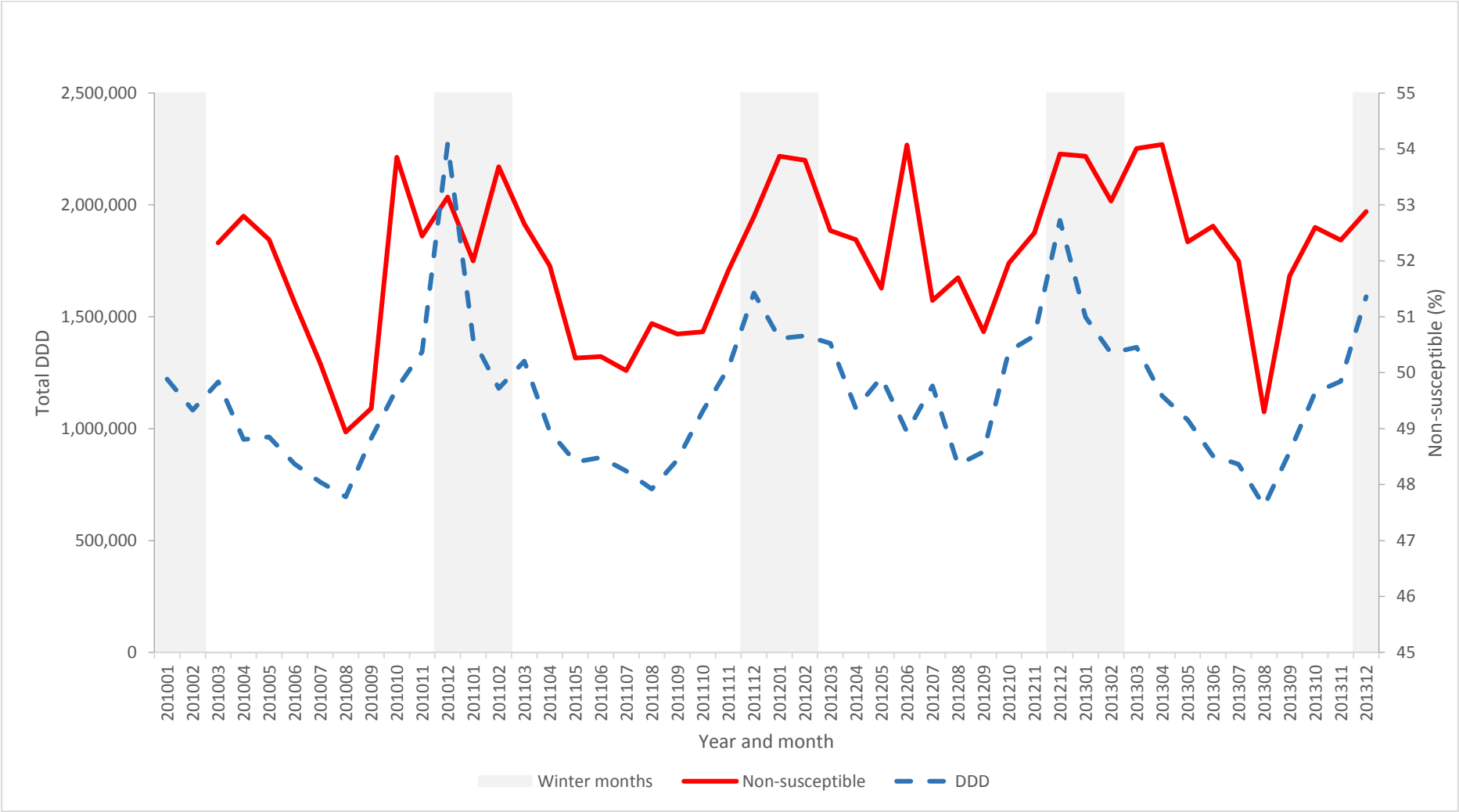

Table 4. Adjusted significant linear associations between antibiotic prescribing and non-susceptibility in E. coli, by current (0) or lagged (negative) quarter

Model no.	Antibiotic non-susceptibility	Antibiotic prescribed	Prescribing period	Adjusted OR (50 DDD unit/1000 population)	95% CI (lower)	95% CI (upper)	*P* value
1	ampicillin / amoxicillin	co-amoxiclav	Quarter 0	1.006	1.002	1.009	0.003
2	ampicillin / amoxicillin	ampicillin / amoxicillin	Quarter 0	1.003	1.001	1.006	0.001
4	co-amoxiclav	ampicillin / amoxicillin	Quarter 0	0.994	0.991	0.998	0.003
			Quarter -3	1.006	1.002	1.009	0.004
			Quarter -4	1.006	1.002	1.009	0.002
5	ciprofloxacin	co-amoxiclav	Quarter 0	0.986	0.975	0.997	0.015
8	ciprofloxacin	fluoroquinolones	Quarter -4	1.033	1.003	1.066	0.034
9	co-amoxiclav	co-amoxiclav	Quarter -3	1.017	1.009	1.026	<0.001
13	nitrofurantoin	cephalexin	Quarter -3	1.041	1.009	1.075	0.013
14	nitrofurantoin	nitrofurantoin	Quarter 0	0.955	0.914	0.997	0.036
			Quarter -1	1.063	1.013	1.115	0.013
			Quarter -4	0.791	0.703	0.890	<0.001
15	trimethoprim	trimethoprim	Quarter 0	0.988	0.978	0.999	0.031
			Quarter -1	1.016	1.004	1.028	0.008
			Quarter -2	1.018	1.006	1.030	0.003
			Quarter -4	1.016	1.005	1.026	0.005

Table 5. Adjusted odds ratio (OR) between single GP practices and antibiotic non-susceptibility of E. coli from urine isolates

Model no.	Antibiotic non-susceptibility	Antibiotic prescribed	Single GP (adjusted OR)	95% CI (lower)	95% CI (upper)	*P* value
1	ampicillin / amoxicillin	co-amoxiclav	1.097	1.027	1.171	0.006
2	ampicillin / amoxicillin	ampicillin / amoxicillin	1.083	1.014	1.156	0.018
3	ampicillin / amoxicillin	fluoroquinolones	1.095	1.024	1.170	0.008
4	co-amoxiclav	ampicillin / amoxicillin	1.361	1.148	1.614	<0.001
5	ciprofloxacin	co-amoxiclav	1.458	1.267	1.676	<0.001
6	ciprofloxacin	ampicillin / amoxicillin	1.448	1.258	1.666	<0.001
7	ciprofloxacin	cephalexin	1.370	1.180	1.592	<0.001
8	ciprofloxacin	fluoroquinolones	1.371	1.182	1.590	<0.001
9	co-amoxiclav	co-amoxiclav	1.398	1.171	1.669	<0.001
10	cephalexin	cephalosporin	1.528	1.322	1.767	<0.001
11	cephalexin	fluoroquinolones	1.534	1.337	1.759	<0.001
12	cephalexin	nitrofurantoin	1.534	1.340	1.756	<0.001
13	nitrofurantoin	cephalexin	1.606	1.304	1.979	<0.001
14	nitrofurantoin	nitrofurantoin	1.657	1.352	2.031	<0.001
15	trimethoprim	trimethoprim	1.110	1.026	1.201	0.009
16	cephalexin	trimethoprim	1.603	1.395	1.841	<0.001