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Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case–control study

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***Background*: To assess the effect of previous antibiotic use on the risk of a resistant *Escherichia coli* urinary tract infection (UTI), we undertook a case–control study with prospective measurement of outcomes in 10 general practices in the UK.**

***Methods*: Urinary samples from all patients with symptoms suggestive of UTIs were sought, and those with a laboratory-proven *E. coli* infection were interviewed and their medical records examined. Case patients were those with ampicillin- or trimethoprim-resistant infections and control patients had infections that were susceptible to antibiotics, including ampicillin and trimethoprim.**

***Results*: Risk of ampicillin-resistant *E. coli* infection in 903 patients was associated with amoxicillin prescriptions of ≥7 days duration in the previous 1 month [odds ratio (OR) = 3.91, 95% CI 1.64–9.34] and previous 2–3 months (2.29, 1.12–4.70) before illness onset. For prescriptions <7 days duration, there was no statistically significant association. Higher doses of amoxicillin were associated with lower risk of ampicillin resistance. For trimethoprim-resistant *E. coli* infections, the OR was 8.44 (3.12–22.86) for prescriptions of trimethoprim of ≥7 days in the previous month and 13.91 (3.32–58.31) for the previous 2–3 months. For trimethoprim prescriptions of <7 days, the OR was 4.03 (1.69–9.59) for the previous month but prescribing in earlier periods was not significantly associated with resistance.**

***Conclusions*: Within the community setting, exposure to antibiotics is a strong risk factor for a resistant *E. coli* UTI. High-dose, shorter-duration antibiotic regimens may reduce the pressure on the emergence of antibiotic resistance.**

Keywords: antibiotics, resistance, UTIs, epidemiology

Introduction

Policies to reduce inappropriate antibiotic prescribing in primary care, thereby reducing the pressure for the emergence and spread of antibiotic-resistant pathogens, have had some success, but substantial variations in prescribing rates between- and within-countries persist.[1–5] One limiting factor is the scepticism expressed by many clinicians about the link between their own antibiotic prescribing and resistant infections in their patients.[6] Current policies are based largely on ecological relationships between prescribing and resistance, and there are only limited data at the level of the individual patient that are not subject to the serious selection bias of using routinely collected patient data and that are adjusted for potential confounders.[7,8] Interventions to improve the quality of antibiotic prescribing could be enhanced if the link between antibiotic prescribing and being infected with a resistant, as opposed to a susceptible, organism at the level of the individual patient could be established, and if the influence of time from prescription to onset of resistant infection, frequency of antibiotic use and duration and dose of antibiotic could be

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quantified. To address this evidence gap, we undertook a nested case–control study of incident cases of clinically suspected urinary tract infections (UTIs) presenting in general practice.

Materials and methods

General practices in South Wales representing the range of geography, social economic deprivation and prescribing rates were recruited and stratified by quartiles for prescribing rates, size, deprivation score and rate of submitting urine samples. Deprivation was assessed by the Townsend score,[9] a measure derived from census data, based on unemployment, car ownership, overcrowding and type of housing tenure. Five practices already participating in surveillance were invited to participate and a further five were selected to ensure a balance across these parameters.

On the basis of the local data, we estimated that 20 000 UTI cases would present to these practices over 18 months, of which at least 2000 would yield *Escherichia coli* infections in urine specimens. From the Wales GP Morbidity Study, we expected that 20% of these specimens would be duplicates. We estimated that we would obtain a 60% response rate from all eligible participants and hence expected approximately 960 patients to take part in our study. After the pilot study, it was estimated that 38% would be susceptible to all antibiotics, defining the controls, and that ~50% would be resistant to ampicillin and 20% to trimethoprim. This would give approximately 500 cases resistant to ampicillin, 200 cases resistant to trimethoprim and 380 controls. Assuming that at least 13% of the population would have had the relevant antibiotic prescribed in the previous year, the study would have at least 90% power for detecting an odds ratio (OR) of 2 for the association between prior antibiotic prescribing and a UTI resistant to that antibiotic.

From July 2002 to March 2004, we sought to enrol all patients presenting at the selected practices with a clinically suspected UTI. Health professionals obtained written informed consent and asked patients to submit urine specimens. Copies of the laboratory results were sent simultaneously to the research team and the practices. A research nurse who was blind to the laboratory results administered a questionnaire about treatment of the current infection, outcomes, history of prior antibiotic exposure, comorbidity, illness history, exposure to others who take antibiotics either in the home or work, household details and socioeconomic factors. Informed consent was sought to review medical records to identify antibiotics prescribed in the year before the UTI for both the patients and other members of their household. The study was approved by the Local Research Ethics Committee in January 2002.

Study patients were those who presented with a new episode of UTI and a laboratory-confirmed ($>10^5$ organisms per mL) *E. coli* infection; catheterized patients and those with UTI in the previous 4 weeks were excluded. Susceptibilities to trimethoprim, ampicillin, co-amoxiclav, cefalexin, ciprofloxacin and nitrofurantoin were reported using the BSAC method.[10] Case patients were those with *E. coli* resistant to ampicillin or trimethoprim and controls were patients whose *E. coli* were susceptible to all six antibiotics tested. A sample of 139 isolates from the 3 participating NHS laboratories were retested at the University Antibiotic Reference Laboratory and all susceptibilities were confirmed.

Statistical analysis

The primary hypothesis was that the odds of being infected with an antibiotic-resistant, compared with an antibiotic-susceptible, *E. coli* would be modified by prior use of the antibiotic to which the organism was resistant and that the extent of this modification would depend on how long before the infection the prior use occurred. A secondary hypothesis was that the odds would depend on the duration of the prescription. These hypotheses were assessed by calculating adjusted ORs using multivariate logistic regression with SPSS v12. The ORs were adjusted for the following clinically relevant variables: age (categorical variable divided into seven groups), gender, practice and previous bladder operation. In order to explore the parameters of 'antibiotic pressure', we recorded the number of prescriptions in the year before the date of the sample for the current UTI and also the date, dosage and duration of each prescription. The duration of a prescription was classified into '<7 days' and 'at least 7 days'. We defined the usage to be concurrent if the date of the prescription was after the date of onset of symptoms. We used the Nagelkerke coefficient of determination to estimate the percentage of variation in resistance explained by the logistic regression models. The goodness-of-fit of each model was assessed using the Hosmer and Lemeshow test. The results were checked using multilevel modelling to account for the hierarchical nature of the sampling but these had very little effect.

Results

Submission of urine specimens by the 10 study practices averaged 8059 per year during the study period. In all, there were 2124 laboratory-confirmed cases of *E. coli*, of which 1508 met the inclusion criteria (496 were duplicate samples and 120 patients did not meet the clinical criteria). Questionnaires were completed for 932 (62%) and medical records were checked for 903 (97%) of these patients. Participating patients were similar in age, gender and general practice to those who declined to participate.

Ampicillin resistance

Of the 903 patients, 359 (40%) had *E. coli* infections resistant to ampicillin and were the cases for this part of the study; 489 (54%) patients had *E. coli* infections susceptible to all antibiotics tested and were the controls. Two hundred and seventeen (24%) had been prescribed 294 courses of amoxicillin during the previous year. Of these, 68% were for respiratory tract infection, 15% for UTI, 3% for oral infection and 14% for other reasons.

Patients with ampicillin-resistant *E. coli* infections were significantly more likely to have been prescribed amoxicillin in the previous year compared with controls (OR 1.70, 1.24–2.32) (Table 1). There was a significant trend in ORs for length of time between the most recent prescription and the date of the sample ($\chi^2 = 17.3$, $P < 0.0001$). For concurrent prescribing compared with no prescribing, the OR was 9.34 (1.12–78.01), falling to 2.59 (1.25–5.40) for the previous month and to 0.90 (0.42–1.93) for 10–12 months previously.

The OR for patients prescribed amoxicillin for at least 7 days in the previous year compared with no antibiotic was 1.79 (1.24–2.58); for <7 days duration, the OR was 1.20 (0.65–2.19).

Ampicillin resistance was significantly associated with the number of amoxicillin prescriptions in the previous 12 months ($\chi^2 = 16.3$, $P < 0.0001$). The ORs increased from 1.44 (1.02–2.05) for one prescription, compared with none, to 2.28 (1.16–4.48) for two prescriptions and to 5.71 (1.58–20.65) for three or more prescriptions.

To investigate the effect of dosage separate from frequency of prescription we compared data from the 171 patients who had

Table 1. Prior amoxicillin prescriptions and risk of ampicillin-resistant *E. coli* UTIs

Variable	Category	Resistant/susceptible	OR	95% CI
Timing of amoxicillin				
amoxicillin in previous 12 months	no	250/389	ref	
	yes	109/100	1.70	1.24–2.32
time period of most recent amoxicillin previous to UTI	1 month (prescribed after reported date of onset concurrent use)	6/1	9.34	1.12–78.01
	1 month (prescribed before reported date of onset previous use)	20/12	2.59	1.25–5.40
	2–3 months	28/21	2.07	1.15–3.73
	4–6 months	19/22	1.34	0.71–2.53
	7–9 months	25/25	1.56	0.87–2.77
	10–12 months	11/19	0.90	0.42–1.93
Duration				
duration of amoxicillin prescription nearest to UTI	none	250/389	ref	
	<7 days	20/26	1.20	0.65–2.19
	7+ days	76/66	1.79	1.24–2.58
Number of amoxicillin courses				
number of amoxicillin courses in previous 12 months	0	250/389	ref	
	1	76/82	1.44	1.02–2.05
	2	22/15	2.28	1.16–4.48
	3+	11/3	5.71	1.58–20.65
Dose of amoxicillin				
amoxicillin dose risk of 250 mg compared with 500 mg, both three times a day, in previous 12 months for subjects who had a single prescription	none	250/389	ref	
	low dose	69/52	2.07	1.39–3.06
	high dose	17/29	0.91	0.49–1.70

received only one prescription in the previous year with those patients who had not received a prescription. The OR for 250 mg of amoxicillin three times daily compared with none was 2.07 (1.39–3.06) but was 0.91 (0.49–1.70) for 500 mg three times daily. The OR comparing low dose with high dose was 2.19 (1.08–4.41).

Interactions between the duration and timing of the most recent amoxicillin prescription were investigated using logistic regression to adjust for age, gender, practice and previous bladder surgery. In the group of patients where the most recent prescription was for <7 days, none of the adjusted ORs was found to be significantly increased (Table 2). The OR was 3.35 for prescribing in the previous month, similar to the unadjusted OR, but in both cases the confidence interval included 1. There was no trend with increasing time since prescription. However, for the group in whom the most recent prescription was for ≥7 days, there was a statistically significant increased risk with prescribing in the previous month (OR 3.91, 1.64–9.34) and for 2–3 months previously (OR 2.29, 1.12–4.70). The results of the Hosmer and Lemeshow test showed that there was no significant lack-of-fit in the logistic regression model ($P = 0.714$). Associations with the total duration of prescriptions in each period were also investigated; results were very similar to those of the most recent prescription. The number of courses prescribed in the previous year did not add significantly to the fit of the model but the dose of amoxicillin could not be explored in the model because of small numbers. We estimated that 6% of the variation in ampicillin resistance was explained by prescribing for amoxicillin in the previous year.

Trimethoprim resistance

Of the 903 patients, 154 (17%) had *E. coli* infections resistant to trimethoprim and were the cases for this part of the study; 489 (54%) were susceptible to all antibiotics tested and were the controls. Two hundred and seven (23%) had been prescribed at least one course of trimethoprim in the previous year; 83% of these were for UTIs.

Patients with trimethoprim-resistant infections were significantly more likely to have been prescribed trimethoprim in the previous year compared with controls (OR 2.39; 1.62–3.53) (Table 3). There was a significant trend in ORs for length of time between the most recent prescription and the date of the sample ($\chi^2 = 30.5$, $P < 0.0001$). The OR was 4.93 (2.61–9.30) for concurrent prescribing compared with no prescribing, falling to 4.11 (0.57–29.53) for the previous month to 1.06 (0.49–2.27) for 4–6 months previously.

There was a significantly increased risk of resistance associated with length of course of trimethoprim compared with no prescription, with ORs of 4.62 (2.73–7.82) for ≥7 days, and 1.60 (0.92–2.77) for <7 days. The ratio of these ORs was 2.89 (1.45–5.79), showing that the OR for the longer course was significantly greater than that for the short course prescription.

Table 2. Logistic regression models relating prior prescriptions to risk of antibiotic-resistant *E. coli* UTIs

	Ampicillin			Trimethoprim		
	proportion-resistant	unadjusted OR[a] (95% CI)	adjusted OR[b] (95% CI)	proportion-resistant	unadjusted OR[a] (95% CI)	adjusted OR[b] (95% CI)
No antibiotics	250/639 (39.1)	reference	reference	94/480 (19.6)	reference	reference
Duration <7 days						
previous month	6/9 (66.7)	3.11 (0.77, 12.56)	3.35 (0.82, 13.72)	11/25 (44)	3.23 (1.42, 7.33)	4.03 (1.69, 9.59)
previous 2–3 months	4/10 (40)	1.04 (0.29, 3.71)	1.04 (0.28, 3.80)	3/10 (30)	1.76 (0.45, 6.93)	1.68 (0.40, 7.09)
previous 4–6 months	3/8 (37.5)	0.93 (0.22, 3.94)	0.65 (0.12, 3.44)	2/19 (10.5)	0.48 (0.11, 2.13)	0.49 (0.10, 2.27)
previous 7–9 months	5/13 (38.5)	0.97 (0.31, 3.01)	0.92 (0.29, 2.94)	4/16 (25.0)	1.37 (0.43, 4.34)	1.97 (0.59, 6.61)
previous 10–12 months	2/6 (33.3)	0.78 (0.14, 4.28)	0.90 (0.16, 5.05)	1/5 (20)	1.03 (0.11, 9.29)	1.46 (0.15, 14.13)
Duration 7+ days						
previous month	17/25 (68)	3.31 (1.41, 7.78)	3.91 (1.64, 9.34)	14/22 (63.6)	7.19 (2.93, 17.63)	8.44 (3.12, 22.86)
previous 2–3 months	22/36 (62.2)	2.45 (1.23, 4.87)	2.29 (1.12, 4.70)	8/11 (72.7)	10.95 (2.85, 42.07)	13.91 (3.32, 58.31)
previous 4–6 months	15/31 (41.1)	1.46 (0.71, 3.00)	1.43 (0.67, 3.05)	6/18 (33.3)	2.05 (0.76, 5.61)	2.32 (0.80, 6.75)
previous 7–9 months	15/30 (50)	1.56 (0.75, 3.24)	1.45 (0.68, 3.07)	5/9 (55.6)	5.13 (1.35, 19.49)	5.50 (1.37, 22.15)
previous 10–12 months	7/20 (35)	0.84 (0.33, 2.13)	0.75 (0.29, 1.95)	3/8 (37.5)	2.46 (0.58, 10.49)	2.84 (0.60, 13.36)

[a]Reference category is no antibiotics.
[b]Adjusted for age, sex, practice and bladder operation.

Table 3. Prior trimethoprim prescriptions and risk of trimethoprim-resistant *E. coli* UTIs

Variable	Category	Resistant/ susceptible	OR	95% CI
Timing of trimethoprim				
trimethoprim in previous 12 months	no	94/386	ref	
	yes	60/103	2.39	1.62–3.53
time period of most recent trimethoprim previous to UTI	1 month prescribed after reported date of onset (concurrent use)	24/20	4.93	2.61–9.30
	1 month (prescribed before reported date of onset previous use)	2/2	4.11	0.57–29.53
	2–3 months	11/14	3.23	1.42–7.33
	4–6 months	9/35	1.06	0.49–2.27
	7–9 months	9/17	2.17	0.94–5.03
	10–12 months	5/15	1.37	0.49–3.86
Duration of trimethoprim				
duration of trimethoprim prescription nearest to UTI	none	94/386	ref	
	<7 days	21/54	1.60	0.92–2.77
	7+ days	36/32	4.62	2.73–7.82
Number of trimethoprim courses				
number of trimethoprim courses in previous 12 months	0	94/386	ref	
	1	41/81	2.08	1.34–3.22
	2	8/16	2.05	0.85–4.94
	3+	11/6	7.53	2.71–20.88

The risk of trimethoprim resistance was significantly associated with the number of prescriptions in the previous 12 months ($\chi^2 = 25.5$, $P < 0.0001$). The ORs increased from 2.08 (1.34–3.22) for one prescription to 2.05 (0.85–4.94) for two prescriptions and 7.53 (2.71–20.88) for three or more prescriptions.

In a logistic regression model, adjusting for age, gender, practice and previous bladder surgery, for those patients who were most recently prescribed trimethoprim for <7 days, a prescription in the previous month was associated with an increased risk (Table 2), with adjusted OR of 4.03 (1.69–9.59). Earlier time periods were not significantly associated with an increased risk and there was no clear trend. For patients who had prescriptions with duration of at least 7 days, there was a statistically significant increased risk of resistance for prescriptions within the previous month (adjusted OR 8.44, 3.12–22.86) and the previous 2–3 months (adjusted OR 13.91, 3.32–58.31). ORs were above 2 for the 4–12 months period but lower confidence limits were above 1 only for the 7–9 months period (OR 5.50, 1.37–22.15). The results of the Hosmer and Lemeshow test showed that there was no significant lack-of-fit in the logistic regression model ($P = 0.742$). Associations with the total duration of prescriptions in each period were also investigated; results were very similar to those of the most recent prescription. The number of courses did not add significantly to the fit of the model. We estimate that 19% of the variation in trimethoprim resistance was explained by prescribing for trimethoprim in the previous year.

Other potential risk factors

We considered associations with usage of other antibiotics. There was no statistically significant association between trimethoprim prescribing in the previous year and ampicillin resistance (OR 1.20, 0.87–1.66) [Table S1, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)]. The association between amoxicillin prescribing and trimethoprim resistance approached statistical significance (OR 1.51, 0.995–2.28). These remained non-significant when added into the multivariate models. Patients prescribed cephalosporins in the year prior to the UTI had a significantly increased risk of trimethoprim resistance (OR 2.10, 1.13–3.90) and of ampicillin resistance (OR 1.99, 1.21–3.28). Cephalosporin usage was marginally significant when added into each multivariate model but did not alter the effect sizes for either amoxicillin prescribing or trimethoprim prescribing. Further analyses of number, timing and duration of cephalosporin prescriptions and associations with resistance were not possible due to small numbers. For those patients who were prescribed a β-lactam (excluding amoxicillin and cephalosporins), the risk of ampicillin resistance was increased but was not statistically significant (OR 1.32, 0.90–1.92) and similarly for trimethoprim resistance (OR 1.22, 0.74–2.01). This remained non-significant when added into each multivariate model and did not alter effect sizes for other variables.

Neither ampicillin nor trimethoprim resistance was significantly associated with gender [Table S2, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)] and there was no consistent pattern in associations between either age or social class and resistance. Neither ampicillin- nor trimethoprim-resistant infections were significantly associated with an infectious illness or a previous UTI (Table S2). Trimethoprim resistance was associated with previous use of a catheter (OR 1.55, 1.03–2.35) and previous bladder surgery (OR 2.05, 1.17–3.60); there was an

increased risk of borderline significance between previous bladder surgery and ampicillin resistance (OR 1.57, 0.98–2.52). Associations with other comorbidities were not statistically significant [Table S2, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)].

Discussion

We found that compared with infection with a susceptible *E. coli* both ampicillin- and trimethoprim-resistant *E. coli* UTIs were associated with amoxicillin and trimethoprim prescriptions of 7 or more days duration in the previous 3 months, but there was no evidence that demographic characteristics, comorbidities or previous clinical history (other than previous bladder operations or use of catheters) were risk factors. In general, the ORs were higher for trimethoprim compared with ampicillin resistance, although the relationships with time were similar. For prescriptions of <7 days duration, the association was significant only for the following month. The frequency of prescription did not improve the explanatory power of the models. Numbers were too small to include dosage in the models, but in univariate analyses the high dose of ampicillin was associated with a significantly lower risk of resistance in comparison with the low dose. It is possible that the cumulative pressure of prescribing throughout a period has a greater effect than the most recent prescription, but the results were very similar when the total duration of prescriptions was used. As the majority of patients had a single prescription, there was limited power for investigating this.

We found some evidence that usage of one antibiotic is associated with resistance to another. For ampicillin usage and trimethoprim resistance, and trimethoprim usage and amoxicillin resistance, the association was not statistically significant but the OR was raised. However, for both ampicillin and trimethoprim resistance, there was a significant association with usage of cephalosporins. Patients who had used those were more likely to have had previous UTIs and their clinical history may have influenced prescribing. The study was not powered to look at cephalosporin resistance, and only four patients who had used cephalosporins in the last year were resistant to cefalexin, so that conclusions regarding cephalosporin usage and resistance cannot be drawn.

The results on usage of one antibiotic and resistance to another do raise interesting questions about the resistance mechanisms involved; do they arise from linkage of genetic material, for example, from plasmids? This cannot be answered by this study, however.

The validity of our findings depends on the accurate designation of cases and controls, defined, respectively, by *E. coli* resistance and susceptibility to antibiotics. Testing was performed in quality-controlled accredited laboratories and there was 100% agreement on re-testing for ampicillin and trimethoprim susceptibilities at the antibiotic reference laboratory. The choice of controls as subjects with UTIs susceptible to all antibiotics was determined by our aim to examine factors that led to resistant infections, taking into account underlying conditions and procedures that might predispose to UTIs. Harris *et al.*[11] have argued that such a choice of controls could lead to bias, because antibiotics for respiratory infections could prevent those with a urinary tract colonization from developing a UTI, and therefore such people would be excluded from being controls. This is rather speculative, not supported by any data and is unlikely to have a significant effect on the results. Measurement of exposure is also important. We equated previous antibiotic prescriptions with exposure to antibiotics. We do not know whether the patients actually took the antibiotics or for how long. Recall of antibiotics used in the previous 12 months was too difficult for many patients and we had to rely on prescription data from their medical records.

The relationship between antibiotic prescribing and the risk of resistant infections has not been well characterized previously at the individual level for patients in the community. Our systematic review of community-acquired UTIs in 2002[7] identified only 10 studies that analysed individual data; a recent update [Table S4, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/), January 2001–week 26 of 2005] identified a further 7 studies.[12–18] Several studies lacked clear case definitions, were often underpowered and did not always control for important confounding factors, and it was not always clear if exposure to antibiotics excluded antibiotics prescribed for the incident UTI. Many relied on routinely submitted urine specimens and so are subject to selection bias, as these samples are likely to include a higher proportion of older, more severely affected patients and patients with failed antibiotic treatment and other special risk factors such as bladder surgery. Findings, therefore, may not be representative of the general population consulting in general practice with UTIs.[19] Several studies involved highly selected groups of patients, such as those attending outpatient clinics and emergency departments,[15–18] used limited data on antibiotic usage[13,14] or combined results from a mixture of different bacterial pathogens.[15]

There are, however, several studies directly relevant to this one. Pedersen *et al.*[20] linked Danish patients with community-acquired *E. coli* bacteraemia to prior prescribing of any antibiotic and found ORs for ampicillin resistance of 2.6 (1.6–4.3), 2.3 (1.4–4.0) and 1.6 (0.8–2.9) for the previous month, 2–3 months and 4–6 months, respectively, compared with no prior use, and for trimethoprim resistance of 4.0 (2.0–7.9), 2.7 (1.3–5.9) and 1.5 (0.6–3.9). They did not examine individual antibiotics, nor their duration or dose. However, their ORs for a different patient population are similar to those of our study on UTIs looking at specific prior use of amoxicillin and trimethoprim.

Steinke *et al.*[12] linked records of routine hospital laboratory and community prescribing data in Scotland and found that Gram-negative bacteria were four times as likely to be trimethoprim-resistant if trimethoprim had been prescribed during the preceding 6 months. These results were not specific to *E. coli* but are similar to those we report here, as were those of a later record linkage study by Donnan *et al.*,[17] who examined trimethoprim resistance in relation to the timing of previous use of trimethoprim. Overall, they found ORs of 1.22 (1.16–1.28) for prior use, 9.19 (6.35–13.3) for 8–15 days before the incident UTI and 2.93 (2.20–3.89) for 16–30 days previously, falling to 1.45 (1.03–2.05) for 4–6 months previously. It is possible that the 8–15 days period included concurrent prescribing, which was identified in our study through patient interviews.

Our study has major methodological strengths compared with these previous studies. We attempted to obtain data on all UTIs presenting at general practices, not just those submitted routinely for laboratory testing, which are likely to be a highly selected subset of all cases. By using a detailed questionnaire, backed up

by an examination of GP records, we were able to obtain a detailed medical history to rule out concurrent prescribing and to examine the influence of comorbidities and other sources of exposure to antibiotics. Although we found a strong association between prescriptions and subsequent resistant infection for both ampicillin and trimethoprim, the proportion of variation that can be explained in the logistic model is not high. Most resistant *E. coli* infections cannot be explained by use of antibiotics by the patients nor by proximity to others taking antibiotics at home or visiting or working in settings where antibiotic use is likely. UTIs generally originate from the patient's own intestine and antibiotics select for resistant organisms in the *E. coli* in the gut. One possible explanation for the association between resistant *E. coli* infections and treatment with lower doses of antibiotics is that lower doses may not be as effective at clearing bacteria with intermediate resistance and thus may allow this population to proliferate. Hay *et al.*[21] found that *E. coli* identified as contaminants of urine samples from asymptomatic adults were more likely to be resistant to amoxicillin and/or trimethoprim if an antibiotic had been prescribed in the previous 2 months, although this effect did not persist over 12 months, and showed a dose–response relationship in the case of trimethoprim use. The potential role of food as a vehicle for antibiotic resistance is another option to be considered.[22]

In summary, we have found that previous prescribing of amoxicillin and trimethoprim for 7 days or more in general practice is associated with an increased risk of ampicillin and trimethoprim resistance in UTIs in the following 3 months and that in the case of ampicillin a higher prescribed dose may reduce this risk. Interventions to deliver more appropriate prescriptions to limit antibiotic resistance should therefore consider the benefits of higher dose, shorter duration courses.

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Transparency declarations

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Supplementary data

Tables S1–S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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