

## Presence of bacteriuria caused by trimethoprim resistant bacteria in patients prescribed antibiotics: multilevel model with practice and individual patient data

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### Abstract

**Objective** To look for evidence of a relation between antibiotic resistance and prescribing by general practitioners by analysis of prescribing at both practice and individual patient level.

**Design** Repeated cross-sectional study in 1995 and 1996.

**Setting** 28 general practices in the Ninewells Hospital laboratory catchment area, Tayside, Scotland.

**Subjects reviewed** 8833 patients registered with the 28 practices who submitted urine samples for analysis.

**Main outcome measures** Resistance to trimethoprim in bacteria isolated from urine samples at practice and individual level simultaneously in a multilevel model.

**Results** Practices showed considerable variation in both the prevalence of trimethoprim resistance (26-50% of bacteria isolated) and trimethoprim prescribing (67-357 prescriptions per 100 practice patients). Although variation in prescribing showed no association with resistance at the practice level after adjustment for other factors ( $P = 0.101$ ), in the multilevel model resistance to trimethoprim was significantly associated with age, sex, and individual-level exposure to trimethoprim ( $P < 0.001$ ) or to other antibiotics ( $P = 0.002$ ). The association with trimethoprim resistance was strongest for people recently exposed to trimethoprim, and there was no association for people with trimethoprim exposure more than six months before the date of the urine sample.

**Discussion** Analysis of practice level data obscured important associations between antibiotic prescribing and resistance. The results support efforts to reduce unnecessary prescribing of antibiotics in the community and show the added value of individual patient data for research on the outcomes of prescribing.

### Introduction

The increasing prevalence of drug resistant bacteria is a major public health problem throughout the world.<sup>1</sup> Prescribers and policy makers require more precise

information about the relation between prescribing and resistance in order to analyse the consequences of prescribing decisions.<sup>2</sup>

In Britain national prescribing data are currently available only at the general practice level, and analyses of these data have shown a weak relation between trimethoprim prescribing and resistance.<sup>3-4</sup> Collection of data about individual patients is technically achievable but is more expensive to collect and analyse than practice level data. In addition, linking of information from multiple data sources and creation of databases containing patient specific information raises important issues of confidentiality.<sup>5</sup> The Copenhagen Recommendations identified the need for research to establish the added value of person specific databases that link prescribing to other clinical information such as antibiotic resistance in order to meet the challenges of data protection legislation in Europe.<sup>6</sup>

The aim of this study was to test the hypothesis that, in comparison with practice level data, analysis of individual patient data would reveal a much stronger association between antibiotic exposure and resistance.

### Methods

#### Study population

The study population was drawn from adults resident in the Tayside region aged  $\geq 35$  years and registered with a general practitioner in the catchment area for Ninewells Hospital laboratory from January 1995 to December 1996 inclusive. The final study population was 166 000 subjects from 28 practices, which is roughly 44% of the population of the Tayside region.

#### Ethics and data protection

This study was done under a set of standard operating procedures governing the use of personal data for research in the Medicines Monitoring Unit (MEMO) of Dundee University and written after the Data Protection Act in 1998 and the recommendations of

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the Caldicott report for implementation of the act in the NHS.

Patient data were anonymised electronically with programs written by MEMO (see [bmj.com](http://bmj.com) for details).

Once the data are anonymised, legally they are not covered by the requirements of the Data Protection Act. However, it has to be possible to re-identify an individual for the purposes of research governance and feedback of important results to professionals and patients. Exemption from the need for written consent for studies that follow agreed standard operating procedures was given by the Tayside Research Ethics Committee and the NHS Caldicott Guardians. In addition, all citizens of Tayside are informed that their electronic health records may be used in teaching, audit, or research through a leaflet distributed to all general practices by NHS Tayside. The leaflet says that individuals can request in writing that their records are not used in this way and that their objections will be respected.

#### Antibiotic resistance

The Ninewells Hospital medical laboratory receives about 45 000 urine samples for analysis from general practices each year. We obtained data on culture and sensitivity tests of these samples electronically.

#### Outcomes

At the practice level, the outcome was the proportion of patients within the practice with urine samples containing trimethoprim resistant bacteria, whereas we coded individuals as having either resistant or sensitive bacteria.

#### Practice characteristics

We obtained prescribing information from the prescription database of MEMO (see [bmj.com](http://bmj.com)).<sup>7</sup> We recorded the number of general practitioners, the ratio of male to female doctors, the number of patients, fundholding status, number of urine samples sent for analysis, and the distance from Ninewells Hospital. We extracted the age and sex distributions for each practice, and the distributions of social deprivation.<sup>8</sup>

#### Patient specific characteristics

These included age, sex, and social deprivation category, number of urine samples sent, and prescribing of trimethoprim, other antibiotics, and a selection of other drugs as general prescribing indicators (hormone replacement therapy, oral contraceptives, benzodiazepines, and selective serotonin reuptake inhibitors).

#### Statistical methods

We analysed the practice level data using multiple logistic regression. The equation allowed for con-

founding and interaction to be examined among the independent variables. A full model was fitted allowing for all significant covariates, along with trimethoprim prescribing (see [bmj.com](http://bmj.com)).

We used MLwiN software for analysis of resistance and prescribing in relation to practice level and patient level factors simultaneously.

## Results

### Practice level results

Of the 28 practices, 11 (39%) were fund holders in 1995 and 17 (61%) in 1996, and six (21%) had only male doctors. The practices' list sizes ranged from 1342 to 10 653. None of these differences in practice characteristics affected the results.

The total number of patients who submitted urine samples was 8833. There was considerable variation between practices in the prevalence of trimethoprim resistance in Gram negative bacteria isolated from urine specimens (from 26% to 50%). There was similar variation in prescribing of trimethoprim (from 67 to 357 prescriptions per 100 practice patients) and of other antibiotics (from 2099 to 6352). However, apparent differences between practices and between years were not statistically significant, with considerable overlap of 95% confidence intervals (see [bmj.com](http://bmj.com)). There was no relation between the number of urine samples sent by a practice and dispensing of trimethoprim or of other antibiotics.

In the multiple logistic adjusted analyses of practice level data from 1995 and 1996, trimethoprim prescribing was not significantly associated with trimethoprim resistance. No other variables than those listed in table 1 were independently associated with trimethoprim resistance after adjustment, either with a stepwise procedure or with fitting a full model.

### Multilevel modelling

In contrast to the practice level analysis, the simultaneous practice and individual level analysis showed many variables to be associated with trimethoprim resistance after adjustment, some highly significant. Older age and being female were both significantly associated with higher prevalence of resistance (table 2). Importantly, exposure to trimethoprim was associated with trimethoprim resistance (odds ratio 1.22 (95% confidence interval 1.16 to 1.28)). Exposure to other antibiotics was less strongly, but still highly significantly, associated with trimethoprim resistance (odds ratio 1.18 (1.06 to 1.32)). There were no significant associations for practice level variables with resistance after allowing for patient level factors; in fact, the variability of resistance due to practice level factors was negligible.

Patients with trimethoprim resistant bacteria were more likely to have been exposed to trimethoprim up to six months before the date of the urine sample (see figure).

## Discussion

We found a strong association between antibiotic prescribing and resistance at the individual patient level that was obscured by analysis of aggregate level data from the same population. A key conclusion is

**Table 1** Adjusted repeated measures model of the relation between prevalence of trimethoprim resistant bacteria in patients' urine samples and drug prescribing and other variables at the practice level (1995-6)

Variables	Odds ratio (95% CI)	P value
More trimethoprim prescriptions (+1000 scripts)	1.01 (0.99 to 1.02)	0.101
Greater percentage of male GPs (+10%)	0.95 (0.92 to 0.97)	<0.001
More urine samples sent for analysis (+100)	1.34 (1.26 to 1.40)	<0.001
More SSRI prescriptions (+1000 scripts)	0.67 (0.61 to 0.82)	<0.001
More HRT prescriptions (+1000 scripts)*	0.61 (0.50 to 0.82)	0.001
More oral contraceptive prescriptions (+1000 scripts)*	0.74 (0.61 to 0.99)	0.022

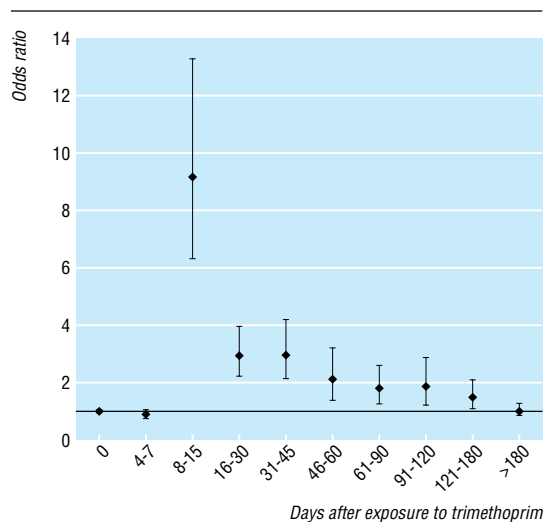
SSRI=selective serotonin reuptake inhibitor. HRT=hormone replacement therapy.  
\*Among female patients only.

that aggregate level studies should not be used to assess the impact of changes in prescribing on resistance. Secondly, every time an antibiotic is prescribed in the community it increases the risk to the individual patient of colonisation by drug resistant bacteria. Thirdly, our results provide important supporting evidence for initiatives to achieve universal electronic prescribing in the NHS, showing the added value of analysis of prescribing data at the individual level.

### Comparison with other studies

We found no relation between antibiotic prescribing and resistance at the general practice level. A systematic review of the literature about trimethoprim resistance and primary care prescribing from 1980 to 2000 identified five studies with area level data, of which only one found a significant relation.<sup>9</sup> A subsequent study of 371 practices in England reported a weak relation between trimethoprim prescribing and resistance.<sup>4</sup> Six case-control studies published before 2001 all showed a strong relation between trimethoprim prescribing and resistance but had inadequate control for population differences in demographics.<sup>9</sup> This review did not include the results of a large case-control study in the Tayside population from 1993 to 1994, which confirmed a strong relation between trimethoprim resistance and prior exposure to trimethoprim or other antibiotics after controlling for other variables.<sup>10</sup>

We found only one other example of a parallel analysis of individual level data and aggregated data about prescribing and resistance.<sup>11</sup> This study, of 35 423 hospital inpatients, reported significant increases in prescribing of antibiotics over a four year period without any apparent change in the prevalence of resistance. However, multiple proportional hazards regression analysis revealed that exposure to a fluoroquinolone, third generation cephalosporin, ampicillin-sulbactam, or imipenem was a strong risk factor for colonisation with bacteria resistant to these drugs.<sup>11</sup>



Odds ratio (95% confidence interval) of trimethoprim exposure in patients with trimethoprim resistant bacteria in urine versus those with sensitive bacteria by days after exposure to trimethoprim

**Table 2** Multilevel model of the relation between presence of trimethoprim resistant bacteria in individual patients' urine samples and drug prescribing and other variables at the practice level and the patient level (1995-6)

Variables	Odds ratio (95% CI)	P value
<b>Patient level factors</b>		
Older age (+10 years)	1.15 (1.13 to 1.17)	<0.001
Year (1996 v 1995)	2.68 (2.14 to 3.35)	<0.001
Sex (male v female)	0.70 (0.59 to 0.82)	<0.001
Sex × year	1.42 (1.11 to 1.82)	0.005
Carstairs deprivation score	0.99 (0.97 to 1.00)	0.096
More urine samples sent for analysis (+1)	1.04 (0.99 to 1.10)	0.106
More trimethoprim prescriptions (+1)	1.22 (1.16 to 1.28)	<0.001
More prescriptions of other antibiotics (+1)	1.18 (1.06 to 1.32)	0.002
Benzodiazepines prescriptions (yes v no)	1.12 (0.68 to 1.83)	0.658
SSRI prescriptions (yes v no)	0.67 (0.34 to 1.32)	0.249
HRT prescriptions (yes v no)*	0.79 (0.64 to 0.97)	0.028
Oral contraceptive prescriptions (yes v no)*	1.01 (0.82 to 1.23)	0.954
<b>Practice level factors†</b>		
Medium practice size (v small)	1.05 (0.90 to 1.22)	0.552
Large practice size (v small)	1.09 (0.93 to 1.27)	0.282
Greater percentage of male GPs (+10%)	0.87 (0.65 to 1.18)	0.381
Fundholding practice (yes v no)	0.96 (0.84 to 1.09)	0.545

SSRI=selective serotonin reuptake inhibitor. HRT=hormone replacement therapy.

\*Among female patients only.

†Practice effect  $\mu_1=0.007$  (SE 0.006)

### Implications of results

The discrepancy between results with individual level data and aggregated data about antibiotic prescribing and resistance is probably largely due to the ecological fallacy.<sup>12</sup> Ecological studies about exposure and outcome are valid only if differences in exposure at the population level accurately reflect differences in exposure to all of the individuals within the populations. With respect to prescribing, large variations in the average consumption of drugs by populations are the product of much greater variation in exposure within the population, and ecological studies of exposure and outcome are therefore fundamentally flawed. Additional problems with aggregated data on prescribing and resistance include sampling bias and inability to control for confounding. Nonetheless, very large ecological studies may reveal associations between antibiotic prescribing and resistance at the population level,<sup>13</sup> and one study suggests that historical antibiotic use in a hospital department and exposure of individual patients to antibiotics are both independent risk factors for infection by drug resistant bacteria.<sup>14</sup>

Our cross sectional study suggests that the influence of trimethoprim prescribing reduces with time, but this needs to be confirmed in longitudinal cohort studies. Most of the available evidence comes from animal studies, which show that resistance persists long after exposure to the antibiotic has ceased, in part because of selective pressure exerted by completely unrelated antibiotics.<sup>15 16</sup> At the population level we know that resistance to individual antibiotics persists in humans long after withdrawal of these drugs from clinical practice,<sup>17 18</sup> but these results are explained by selection by related antibiotics that are still in use. We need more information from longitudinal human studies at the individual level<sup>19</sup> to understand how the process of intestinal colonisation and persistence can be influenced by antibiotic control and by other measures.<sup>20</sup> The ability of primary care computing systems to produce high

**What is already known on this topic**

UK national prescribing data are usually available only at the practice level, and analysis of these data has shown a weak relation between antibiotic prescribing and drug resistance in infective organisms

Such analyses probably suffer from ecological bias, which arises when area level data obscure important associations between individual exposure and risk

**What this study adds**

At the practice level, there was no association between variation in antibiotic prescribing and resistance after adjustment for practice level factors such as fundholding status

Inclusion of individual prescribing data in a multilevel model revealed a highly significant association between exposure to trimethoprim or other antibiotics, particularly in the previous six months, and resistance to trimethoprim

These results show that recent antibiotic exposure increases the risk of colonisation or infection by drug resistant bacteria and show the added value of analysis of data about individual patient prescribing

quality, patient specific data is increasing in Britain and elsewhere,<sup>21</sup> though the use of data may be restricted by legislation.<sup>22</sup>

**Conclusion**

Our results support efforts to reduce unnecessary prescribing of antibiotics in the community.<sup>23</sup> Clear demonstration of the added value of individual data will be important in the debate about practical and reasonable methods for obtaining consent for record linkage research.<sup>24 25</sup>

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Competing interests: TMM serves on advisory boards for Pfizer, Pharmacia, and Novartis but none relating to the current topic. PGD serves on advisory boards about antibiotic prescribing and resistance for Aventis and Pharmacia.

Ethical approval: The study protocol was approved by Tayside Research Ethics Committee.

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**Commentary: Legal issues of data anonymisation in research**

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In this paper Donnan et al expertly demonstrate the value of anonymised individual data in medical research, showing that effects masked in aggregated data are clearly visible when individual data are used. However, the use of anonymised data raises interesting legal questions.

The MEMO researchers paid careful attention to protecting patient confidentiality for the 166 000 files

they used in the study, with the data being anonymised with purpose made software that was used by named staff whose employment contracts could be revoked in the event of breaches of patient confidentiality. Given the large amount of data involved, patients' individual consent could not be sought, but efforts were made to inform patients of the possible use of their medical data and their rights of privacy through the