

Containing antibiotic resistance: decreased antibiotic-resistant coliform urinary tract infections with reduction in antibiotic prescribing by general practices

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ABSTRACT

Background

GPs are urged to prescribe antibiotics less frequently, despite lack of evidence linking reduced antibiotic prescribing with reductions in resistance at a local level.

Aim

To investigate associations between changes in antibiotic dispensing and changes in antibiotic resistance at general-practice level.

Design of study

Seven-year study of dispensed antibiotics and antibiotic resistance in coliform isolates from urine samples routinely submitted from general practice.

Setting

General practices in Wales.

Method

Multilevel modelling of trends in resistance to ampicillin and trimethoprim, and changes in practice total antibiotic dispensing and amoxicillin and trimethoprim dispensing.

Results

The primary analysis included data on 164 225 coliform isolates from urine samples submitted from 240 general practices over the 7-year study period. These practices served a population of 1.7 million patients. The quartile of practices that had the greatest decrease in total antibiotic dispensing demonstrated a 5.2% reduction in ampicillin resistance over the 7-year period with changes of 0.4%, 2.4%, and -0.3% in the other three quartiles. There was a statistically significant overall decrease in ampicillin resistance of 1.03% (95% confidence interval [CI] = 0.37 to 1.67%) per decrease of 50 amoxicillin items dispensed per 1000 patients per annum. There were also significant reductions in trimethoprim resistance in the two quartiles of practices that reduced total antibiotic dispensing most compared with those that reduced it least, with an overall decrease in trimethoprim resistance of 1.08% (95% CI = 0.065 to 2.10%) per decrease of 20 trimethoprim items dispensed per 1000 patients per annum. Main findings were confirmed by secondary analyses of 256 370 isolates from 527 practices that contributed data at some point during the study period.

Conclusion

Reducing antibiotic dispensing at general-practice level is associated with reduced local antibiotic resistance. These findings should further encourage clinicians and patients to use antibiotics conservatively.

Keywords

antibiotic prescribing; antibiotic resistance; primary care; urinary tract infection.

INTRODUCTION

Antibiotic resistance is a major threat to public health,¹ and has risen among many common community-acquired bacterial pathogens, including urinary tract pathogens.^{2,3} Recent antibiotic use is one of the strongest risk factors for infection with antibiotic resistant organisms.⁴ Urinary tract infections (UTIs) caused by antibiotic resistant *Escherichia coli* are symptomatic for longer than UTIs caused by sensitive organisms, and increase workload in general practice.⁵

National and international initiatives have encouraged a more conservative approach to antibiotic prescribing. This approach is based on the assumption that if resistant bacteria are 'less fit' than sensitive strains, reduced exposure to antibiotics will reduce selection pressure, limiting the rise in resistance, and potentially resulting in reduced resistance.⁶ Many initiatives have been directed at general practices to address this issue,

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How this fits in

The association between antibiotic prescribing and antibiotic resistance international and regional levels has been well described. However, there is limited evidence linking reductions in antibiotic prescribing with reductions in antibiotic resistance, especially at a local or practice level. Some suggest that reducing antibiotic prescribing is unlikely to lead to reductions in antibiotic resistance. GPs are urged to prescribe antibiotics less frequently, based on the assumption that resistant organisms are less fit than sensitive ones, and will die out in the face of reduced selection pressure from antibiotics. This is the first large scale study to demonstrate an association between reductions in antibiotic prescribing with reduced antibiotic resistance at the level of general practice. The findings should encourage clinicians, patients, and policy makers to strive for ways to enhance the quality of antibiotic prescribing decisions in primary care.

for example, those delivered by prescribing advisors and academic detailers.⁷

The number of antibiotics prescribed in ambulatory care in western countries has fallen;⁸ however, considerable within- and between-country variations in patterns of community antibiotic prescribing remain. In some countries, notably the US, prescribing of broad spectrum oral antibiotics as a proportion of all oral antibiotics has increased significantly.⁹ Further reductions in community antibiotic prescribing could certainly be achieved if such reductions are shown to be worthwhile.

GPs prescribe approximately 80% of all antibiotics, about half of which are unlikely to benefit patients.¹⁰ Some GPs question their ability to contribute to reductions in antibiotic resistance through changing their prescribing behaviour.^{11,12} Others have challenged the notion that widespread reductions in antibiotic prescribing will be automatically followed by a reduction in resistance, arguing that the acquisition of resistance determinants may have less impact on microbial fitness than previously thought.¹³⁻¹⁵

There is only limited evidence linking reductions in antibiotic prescribing by general practices with reduced local levels of antibiotic resistance.¹⁶ The absence of strong evidence has led to suggestions that attempts to discover new antibiotics are more important than promoting more prudent antibiotic use.

This study aimed to explore the relationship between reductions in dispensed antibiotics at the level of general practice and antibiotic resistant isolates in urine samples submitted from general practice. Specimens from patients with UTIs were used, as urine samples are the most common specimens submitted from primary care for microbial culture and susceptibility analysis. In addition, urinary tract symptoms constitute a significant

workload for general practice, accounting for between 1 and 3% of consultations¹⁷ and represent 15% of all community prescriptions for antibiotics.¹⁸

METHOD

Data

Prescribing. Data on the number of antibiotic items dispensed for each practice, derived from pharmacy reimbursement claims, were obtained from Health Solutions Wales (an NHS Wales organisation responsible for a wide range of specialist services). This organisation provided the number of prescriptions dispensed per quarter for oral formulations of antibiotic groups (broad spectrum penicillins, cephalosporins and cephamycins, and other β -lactams, macrolides, tetracyclines, and quinolones) and individual antibiotic agents (amoxicillin, co-amoxiclav, flucloxacillin, phenoxymethylpenicillin, cefalexin, cefaclor, ceferoxime, erythromycin, clarithromycin, oxytetracycline, ciprofloxacin, nitrofurantoin, and trimethoprim).

Demographic data. Health Solutions Wales also provided practice demographic data on the number of patients registered and the number of GPs per practice. Dispensed antibiotic rates per 1000 registered patients per annum were calculated for each quarter for each of the antibiotics listed above and for antibiotic groups, including β -lactams and broad spectrum penicillins, as well as for total dispensing of the agents listed, referred to as 'total antibiotic dispensing' for simplicity.

Townsend scores were used to measure social deprivation. This score is routinely calculated for the 865 electoral divisions in Wales using census data on unemployment, home and car ownership, and overcrowding.¹⁹ Townsend scores have a mean of 0 and a standard deviation of approximately 4 across electoral divisions. To estimate the level of deprivation of practice areas, researchers created a matrix tabulating the number of registered patients for each practice against patients' residence in electoral divisions (based on individual patients' postcodes). Each electoral division Townsend score calculated from 2001 Census data was weighted using the proportion of the practice population from that electoral division. Practices were then divided into quartiles based on these Townsend scores.

Isolates. Microbiological data for samples submitted by Welsh general practices were requested from Public Health Laboratories in Abergavenny, Aberystwyth, Bangor, Cardiff, Carmarthen, Rhyl, and Swansea; and from NHS laboratories at the Royal Glamorgan, Prince

Charles, Prince Phillip, Princess of Wales, Royal Gwent, Withybush, and Wrexham Maelor hospitals for the period from April 1996 to March 2003. Not all laboratories were able to supply data for the whole study period because of computing difficulties. Additional data on samples submitted by Welsh general practices in this period were obtained from English laboratories in Chester, Shrewsbury, and Hereford. For each isolate reported as *E. coli* or lactose-fermenting coliform (referred to collectively as coliforms), researchers obtained date of isolation, surgery address, specimen type, hospital number, age and sex of patient, specimen number, organism isolated, and susceptibility results for the following agents (where tested): ampicillin, co-amoxiclav, cefalexin (for six laboratories, cephadrine for the others), trimethoprim, ciprofloxacin (norfloxacin for one laboratory), and nitrofurantoin. Resistance data were linked to the general practice submitting the sample, but it was not possible to link these data to individual GPs within a practice.

Age and sex data were available for each sample, but these could only be linked to practice antibiotic dispensing, rather than dispensing to individual patients. Laboratories were not able to supply consistent data on the overall numbers of urine samples submitted from general practices. They were only able to provide consistent data on samples that were positive for coliforms.

Exclusions

Isolates from catheterised patients were excluded. Resistance to antibiotics where there had been changes in testing methods that might have led to apparent changes in resistance, for example co-amoxiclav, were not considered. Duplicate isolates were defined as repeat isolates with the same susceptibility pattern from the same patient within 91 days of the first isolate with that pattern. These were identified by a macro routine and were excluded from the main analysis. The analysis was repeated and included duplicates to test the sensitivity of results.

Statistical analysis

The primary analysis used only those practices for which consistent resistance data were available for the full 7 years. These were divided into quartiles based on their changes in rates of total antibiotic dispensing between study years 1 and 7; and also based on amoxicillin dispensing and trimethoprim dispensing. Changes in the percentage of resistant strains between years 1 and 7 were compared between these quartiles. Researchers explored whether included practices were systematically

different from excluded practices by comparing patterns in dispensed antibiotics and resistance levels at the end of the study period.

Multilevel modelling was used to analyse the longitudinal pattern of resistance changes and dispensed antibiotics more closely, using data from all study years.

Multilevel modelling partitions variation into different levels in a hierarchy and allows explanatory variables to be entered at appropriate levels of the hierarchy. Three levels were used in the analysis: quarterly results nested within general practices, which in turn are nested within primary care organisations (local health boards in Wales). A term was included in the model to reflect linear trend throughout the study period, and terms were included for quartiles of changes in total antibiotic dispensing. Interactions between the quartiles and study year were modelled to allow for different time patterns in different quartiles.

Trend was modelled as a linear term but in a sensitivity analysis trend was modelled as a series of indicator variables, one for each year, rather than assuming a linear or other specific model. Interactions between quartile and year, practice area deprivation, and other practice characteristics were incorporated in the model.

Secondary analyses used all available data from the 527 practices that contributed data at any point during the 7-year period and not just from the 240 practices for which complete 7-year data were available. Statistical analyses were undertaken using SPSS (version 2.0) and MLwiN (version 2.02).

RESULTS

Microbiology data

Ten laboratories supplied resistance data from year 1; one more began to supply data in each of years 2, 3, and 4 respectively; and a further three only supplied data in years 6 and 7 of the study. In the whole 7-year period there were sensitivity results on 284 227 coliform isolates, rising from 24 548 in year 1 to 51 430 in year 7 as more laboratories provided data. The rate of coliform isolates tested for sensitivity increased from 12.2 to 13.8 per 1000 patients per year. Of these isolates, 24 580 were classed as duplicates and were excluded from the main analysis, but included in a sensitivity analysis.

Although testing practices differed between laboratories, more than 98% of coliform isolates were tested for resistance to ampicillin and trimethoprim and more than 85% for resistance to co-amoxiclav, cefalexin, nitrofurantoin, and a fluoroquinolone; most laboratories tested for resistance to ciprofloxacin, but one laboratory tested for resistance to norfloxacin instead.

Table 1. Median number of dispensed antibiotic items/1000 practice population/year in 240 study practices.

	Year 1	Year 7	Decrease, %
Amoxicillin	328	230	30
Co-amoxiclav	63	41	35
Flucloxacillin	43	62	-43 ^a
Penicillin	78	54	31
Cephalosporins	88	48	45
Macrolides	110	81	26
Trimethoprim	58	60	-3 ^a
Tetracyclines	54	50	8
Quinolones	23	19	19
Nitrofurantoin	7	6	12
Total	881	641	27

^aIndicates an increase.

Overall, 51.6% of the isolates were resistant to ampicillin, 26.1% to trimethoprim, 11.7% to co-amoxiclav, 6.4% to cefalexin, 1.7% to quinolones, and 7.1% to nitrofurantoin, with 58.9% resistant to at least one antibiotic. There were notable differences between laboratories, with ampicillin resistance varying from 43.9 to 57.5%, and trimethoprim resistance varying from 22.7 to 28.4%. These differences were highly significant statistically ($P < 0.00001$), as the number of samples involved is large.

Primary analysis

Resistance data were obtained for 527 practices for at least a part of the study period, but complete resistance data for the entire 7-year study period was only available for 240 of these, due to technical computing problems at some laboratories. The 240

practices were used in the primary analyses. They included a total registered population of approximately 1.7 million patients per study year: more than half the total population of Wales. The mean list size was 7000 and the mean number of whole-time equivalent GPs was 3.75. No practice from North Wales was included in this primary analysis as data from there only became available from the second study year.

Included practices had slightly lower levels of total antibiotic dispensing than excluded practices: 920 items per 1000 for those included in year 1 compared with 1010 per 1000 for those excluded; and 659 per 1000 for those included in year 7, compared with 687 per 1000 for those excluded. Mean level of resistance to ampicillin in year 7 was 51.2% for included practices, compared with 50.4% for excluded practices. Corresponding figures for trimethoprim resistance were 25.0% and 23.6%. Mean Townsend score for included practices was -0.22, and -0.02 for excluded practices. Therefore, practices were reasonably representative in terms of demographics, dispensed antibiotics, and resistance.

The total number of isolates included in the primary analysis was 164 225, increasing from 20 364 in year 1 to 24 382 in year 7. There were reductions in the dispensing of all antibiotics except for flucloxacillin and trimethoprim during the study period (Table 1). Only 5% of the 240 practices increased the rate of total antibiotic dispensing, while 8% increased dispensing for amoxicillin. Quartiles 1 to 4, based on changes in total antibiotic dispensing, were defined according to the values shown in the final row of Table 2: quartile 1 refers to practices that reduced dispensing the most and quartile 4 refers to practices that reduced it least.

Quartile 1 reduced dispensing by at least 371 items per 1000 patients per year; quartile 2 by between 218 and 371; quartile 3 by between 129 and 218; and quartile 4 by less than 129 items per 1000 patients per year. The table also shows 5th and 95th percentiles to emphasise the notable inter-practice variation in these changes of dispensing.

Quartile 1 had a reduction in ampicillin resistance of 5.2% (95% CI = 2.9 to 7.4%). This was the greatest reduction in ampicillin resistance of all the practice quartiles. Quartile 4 had a reduction in ampicillin resistance of only 0.3% (95% CI = -1.4 to 2.0%). For trimethoprim resistance, quartile 1 had a reduction of 3.4% (95% CI = 1.3 to 5.4%) compared to a reduction of 0.8% (95% CI = -0.7 to 2.3%) for quartile 4 (Table 3). The difference between decreases in ampicillin resistance in the first and fourth practice quartiles was 4.9% (95% CI

Table 2. Quartiles with 5th and 95th percentiles for decrease in dispensed antibiotics rates per 1000 patients per year between years 1 and 7.

	Percentile				
	95th	75th	50th	25th	5th
Amoxicillin	637	178	91	44	-17
Co-amoxiclav	118	42	20	3	-1
Flucloxacillin	12	-6	-16	-29	-56
Penicillin	70	40	23	4	-27
Cephalosporins	148	70	34	11	-30
Macrolides	129	53	22	3	-27
Trimethoprim	42	9	-3	-13	-33
Quinolones	38	13	3	-4	-16
Nitrofurantoin	19	5	1	-2	-9
Total	637	371	218	129	3

Negative values indicate increases from years 1 to 7.

Table 3. Reduction (%) in resistance to ampicillin and trimethoprim over a 7-year period, by quartile of reductions in total antibiotic dispensing.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Overall
Ampicillin					
Year 1, %	58.7	50.6	49.2	50.0	51.3
Year 7, %	53.5	51.0	51.6	49.7	51.2
Reduction, % (95% CI)	5.2 (2.9 to 7.4)	-0.4 (-2.3 to 1.5)	-2.4 (-4.1 to -0.7)	0.3 (-1.4 to 2.0)	0.0 (-0.9 to 1.0)
Trimethoprim					
Year 1, %	29.1	26.6	26.5	25.5	25.5
Year 7, %	25.7	24.9	25.0	24.7	25.0
Reduction, % (95% CI)	3.4 (1.3 to 5.4)	1.7 (0.1 to 3.3)	1.5 (0.0 to 2.9)	0.8 (-0.7 to 2.3)	0.4 (-0.8 to 1.7)

= 2.0 to 7.7%; $P = 0.001$). The corresponding difference for trimethoprim resistance was 2.6% (95% CI = 0.6 to 5.1%; $P = 0.045$).

To estimate the effect of the change in dispensing and to estimate the variation attributable to practice and primary care organisation levels, a multilevel linear model was fitted with the actual change in resistance rates as the outcome. For ampicillin there was a statistically significant overall decrease in resistance of 1.15% (95% CI = 0.37 to 1.89%) per decrease of 100 antibiotic items dispensed per 1000 patients per annum.

Polynomial regression was also used to allow for a non-linear relationship, but there was no evidence to suggest non-linearity. Including practice deprivation in the model did not lead to a significant improvement. Fourteen per cent of the variation in resistance changes was attributable to differences between primary care organisations, and 86% to differences between practices. There was a statistically significant overall decrease in resistance of 1.03% (95% CI = 0.37 to 1.67%; $P = 0.0015$) per decrease of 50 amoxicillin items dispensed per 1000 patients per annum.

A similar analysis was performed for changes in trimethoprim resistance. The association with changes in dispensed antibiotics was positive but not statistically significant, with an estimated decrease of 0.58% (95% CI = -0.08 to 1.13; $P = 0.053$) per decrease of 100 items dispensed per 1000 patients per annum. There was, however, a statistically significant overall decrease in resistance of 1.08% (95% CI = 0.06 to 2.10%; $P = 0.034$) per decrease of 20 trimethoprim items dispensed per 1000 patients per annum.

Secondary analysis

The primary analysis included only the 240 practices for which data were available throughout the whole study period. For the secondary analysis, all practices that contributed resistance data at any time were included; this involved 256 370 coliform isolates. To make use of data from all practices, a

three-level multilevel model was fitted with resistance to ampicillin in a quarter as the outcome, and including study year as a linear term with dispensed antibiotics changes summarised by quartiles of change, and including interactions with the quartiles. This showed that the differences between the quartiles were highly significant. The estimated annual rates of decrease from this regression model were 0.46% in quartile 1, and 0.28%, 0.22%, and -0.27% in quartiles 2, 3, and 4 respectively, with resistance increasing in the quartile that reduced amoxicillin dispensing the least (quartile 4).

Practice area deprivation, using Townsend quartiles, was also included in this model. There was a clear increase in the rate of resistance with deprivation, with levels 6% higher in the most deprived quartile, but there was no interaction between deprivation quartiles and quartiles based on changes in dispensed antibiotics. Similar results were obtained for quartiles based on changes in total antibiotic dispensing.

This model assumed a linear trend; as an alternative, year of study was treated as a categorical variable and interactions between the categories and the dispensed antibiotics quartile were also included. While the statistical fit of the model was slightly better, the extra complications in interpreting such a model, including 27 terms related to the study year and dispensed antibiotics quartiles, led researchers to consider the linear model.

A similar analysis was performed for trimethoprim resistance. Rates of decrease of resistance per annum were 0.62%, 0.28%, 0.22%, and -0.27%, with a steady trend from the greatest decrease in the quartile which reduced trimethoprim dispensing most to an increase in the quartile which reduced it least. Deprivation played a smaller part than for ampicillin but there was greater resistance in the most deprived quartile of practices. Similar results were obtained using quartiles based on changes in total antibiotic dispensing.

These analyses excluded duplicate samples but were repeated for the whole set of data, including the duplicates. There was no substantive difference between the two sets of results.

Although information on the rates of submissions of samples by practices was not consistently available, consistent data were obtained on the rate of samples positive for coliforms per 1000 registered patients. Numbers increased in each quartile, with similar patterns for all quartiles, regardless of changes in dispensed antibiotics. For example, in quartile 1 the rate of samples positive for coliforms increased by 2.60 per 1000 registered patients per year, compared with 2.28 in quartile 4.

DISCUSSION

Summary of main findings

The potential effectiveness of reducing antibiotic prescribing to contain antibiotic resistance has been questioned.^{6,15} The main analysis of this study included 164 225 coliform isolates in urine samples undergoing susceptibility testing submitted over a 7-year period by 240 general practices providing care for an annual mean of 1.7 million patients. General practices with the greatest reduction in dispensed antibiotics showed a significant reduction in antibiotic resistance to ampicillin and trimethoprim compared with practices that reduced dispensed antibiotics the least. Levels of ampicillin resistance in those practices which reduced dispensed antibiotics most fell by about 1% per annum; the corresponding figure for trimethoprim was 0.6% per annum. There was a statistically significant overall decrease in ampicillin resistance of 1.03% (95% CI = 0.37 to 1.67%) per decrease of 50 amoxicillin items dispensed per 1000 patients per annum; for trimethoprim resistance the decrease was 1.08% (95% CI = 0.06 to 2.10%) per decrease of 20 trimethoprim items dispensed per 1000 patients per annum.

Strengths and limitations of the study

The main analysis included only those practices for which data on complete dispensed antibiotics and microbiology were available for the whole 7-year study period. Thus, no new practice began contributing data and no practice stopped contributing data part way through the study period. Therefore, the main analyses included data from only 240 out of a possible 527 general practices, covering a population at risk of 1.7 million people over 7 years. While the included practices were not entirely representative of the whole of Wales, they were broadly similar to the remaining Welsh practices in their pattern of dispensed antibiotics and in their levels of

antibiotic resistance in urine samples during periods when these data were available for excluded practices. Secondary analysis was conducted using all available data (527 practices, 3 million population, 256 370 isolates) and the results were comparable.

Routinely collected data on dispensed antibiotics and microbiology data from routinely submitted samples were used. Clinicians vary in their practice of requesting laboratory analysis of urine samples. Systematic sampling of all patients with symptoms suggestive of UTI would have been ideal, but was not feasible on this scale over such a long period. However, in a smaller study in Wales, where the current researchers attempted systematic sampling by asking all clinicians to request a urine sample for all patients with symptoms suggestive of UTI, ampicillin and trimethoprim resistance rates were similar to the findings in the present study.²⁰

The number of urinary specimens yielding coliforms per 1000 practice population increased by about 17% during the study period. Laboratory procedures and techniques may have improved for identifying coliforms, the incidence of coliform UTIs may have increased during the study period, or sampling thresholds may have fallen. Practices in all quartiles of changes of total dispensed antibiotics showed increased rates of specimens yielding coliform isolates, and so it is unlikely that this increase in the number of positive samples could lead to the differential resistance changes reported here.

The current findings might be explained theoretically by differential changes in GPs' sampling behaviour localised to certain general practices grouped by changes in prescribing patterns. For example, practices that reduced dispensing the most would have had to change their habits in submitting samples so that relatively fewer resistant isolates were identified, perhaps by lowering their threshold for submitting urine samples. The patterns of submission of samples that were positive for coliforms did not change according to patterns of changes in antibiotic dispensing, so this seems unlikely. This study was not able to assess changes in rates of submission of total numbers of urine specimens for each practice, as consistent data on these were not available.

The study sought to identify changes in laboratory methods that might influence levels of reported antibiotic resistance. This led to the exclusion of co-amoxiclav resistance from main analyses. There was no evidence of such changes in testing for resistance to ampicillin or trimethoprim. Fluoroquinolone resistance was not included in the analysis as this is still a relatively

rare phenomenon in urine samples submitted from primary care in Wales.

Given the increase in the practice of 'delayed prescribing', the amount of dispensed antibiotics at practice level is a proxy for antibiotic consumption in those patients from whom specimens were submitted. The amount of dispensed antibiotics is the closest available proxy for antibiotic consumption, but data on individual usage were not available. The effect of this is almost certainly to weaken apparent associations between usage and resistance and so the effects reported here are likely to be underestimates of the true ones. The authors do not suggest that these data can be used to make predictions about antibiotic use and antibiotic resistance in individual patients.²¹

This research was conducted in Wales because of the unique opportunity afforded by the available data sets. There does not appear to be anything unique about Welsh general practices that would limit the applicability of these findings to other settings.

Comparison with existing literature

The association between overall antibiotic use in the community and antibiotic resistance has been well described at European,²² country,⁸ regional,²³ general practice,²⁴ and individual levels.²⁴⁻²⁸ However, few studies have demonstrated that reductions in antibiotic prescribing are associated with reduced levels of antibiotic resistance in the community.

At the country level, reductions in macrolide use were associated with reductions in isolates of resistant *Streptococcus pyogenes* in Japan²⁹ and Finland.³⁰ In Iceland the prevalence of penicillin-resistant pneumococci isolates reduced after a campaign to reduce antibiotic prescribing for children.²⁸ Some of these reductions in resistance may have been associated with the natural decline of a specific clone.^{31,32} Clonality is likely to demonstrate geographical clustering and is unlikely to have played a part in the results of this study, where practices were grouped by changes in practice dispensing rates rather than geographical location.

A controlled study in France showed that an education intervention resulted in fewer antibiotics being prescribed in a community setting. This led to significant reductions in rates of colonisation with penicillin G-nonsusceptible *Streptococcus pneumoniae* in children.³³ Vardhan and colleagues examined trends in penicillin resistant pneumococcal isolates in relation to trends in antibiotics dispensed to 549 patients in Merseyside between 1987 and 2000.³⁴ A reduction in the proportion of resistant-to-sensitive isolates

coincided with a reduction in dispensed antibiotics. There is mixed evidence linking changes in antibiotic use in hospitals with *E. coli* resistance.^{35,36}

To the authors' knowledge, this is the first large scale observational study demonstrating an association between reductions in the rate of antibiotic dispensing at the level of general practice and reduced levels of antibiotic resistance.

Implications for clinical practice and future research

Some may question the clinical significance of these findings, for example, by suggesting that a 2% reduction in trimethoprim resistance may not be worth the effort required to achieve a reduction of 40 dispensed trimethoprim prescriptions per 1000 registered patients per annum. However, this decline in resistance may be sustained, preserving the international reservoir of antibiotic susceptibility.

Demonstrating small changes in resistance in routine clinical urine samples that yield coliforms might be a poor reflection of the true changes in resistance in the community, especially when taking into account that this study examined antibiotic dispensing at the level of general practice. If the study examined the longitudinal association between antibiotic use and antibiotic resistance in individual patients, then the association is likely to have been stronger, given the association between the recent use of certain antibiotics and antibiotic resistance.^{37,38}

Future research should aim for individual-level analysis once it is possible to link individual clinical, microbiology, and prescribing records on a large scale. Qualitative research suggests that GPs are likely to achieve greater focus on this issue if it could be shown that their efforts have an effect locally.¹¹ Reducing unnecessary antibiotic prescribing also reduces unnecessary risk from side effects and impacts favourably on help-seeking behaviour for respiratory tract infections.³⁹

Interventions aimed at improving the quality of antibiotic prescribing in primary care are often focused at the level of general practice, and their rationale is usually the containment of antibiotic resistance. Until now, there has been little evidence linking reductions in antibiotic prescribing in the community with reduced antibiotic resistance locally. Despite theoretical considerations about why antibiotic resistance might be reversed slowly or even not at all in the community,^{14,15,27,40} the current results demonstrate that reductions in antibiotic prescribing are associated with reduced antibiotic resistance at a practice level, and should encourage patients, clinicians, and policy makers to use antibiotics more conservatively.

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Ethics committee

The Local Research Ethics Committee approved the study (MREC 00/9/39)

Competing interests

The authors have stated that there are none.

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