Antibacterial prescribing and antibacterial resistance in English general practice: cross sectional study

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Abstract

Objective To quantify the relation between community based antibacterial prescribing and antibacterial resistance in community acquired disease.

Design Cross sectional study of antibacterial prescribing and antibacterial resistance of routine isolates within individual practices and primary care groups.

Setting 405 general practices (38 groups) in south west and north west England.

Main outcome measures Correlation between antibacterial prescribing and resistance for urinary coliforms and *Streptococcus pneumoniae*.

Results Antibacterial resistance in urinary coliform isolates is common but the correlation with prescribing rates was relatively low for individual practices (ampicillin and amoxicillin $r_s = 0.20$, $P = 0.001$; trimethoprim $r_s = 0.24$, $P = 0.0001$) and primary care groups (ampicillin and amoxicillin $r_s = 0.44$, $P = 0.05$; trimethoprim $r_s = 0.31$, $P = 0.09$). Regression coefficients were also low; a practice prescribing 20% less ampicillin and amoxicillin than average would have about 1% fewer resistant isolates (0.94/100; 95% confidence interval 0.02 to 1.85). Resistance of *S pneumoniae* to both penicillin and erythromycin remains uncommon, and no clear relation with prescribing was found.

Conclusions Routine microbiological isolates should not be used for surveillance of antibacterial resistance in the community or for monitoring the outcome of any change in antibacterial prescribing by general practitioners. Trying to reduce the overall level of antibiotic prescribing in UK general practice may not be the most effective strategy for reducing resistance in the community.

Introduction

The threat of increasing antimicrobial resistance is causing concern internationally.[1] Much of the world market for antimicrobial drugs is for community use ($12bn (£8000m) of $17bn in 1997),[2] and many voices have called for a reduction in community prescribing.[3–5] In the United Kingdom, the government has recently launched an initiative to monitor and limit antimicrobial prescribing in general practice on the assumption that this will reduce resistance.[6] The probability of an individual being infected by a resistant organism is known to be increased by recent use of an antibacterial drug,[7] and studies in Iceland and Finland have shown that the level of prescribing in the community increases the odds of resistance in individual commensal[8] and pathogenic[9] organisms.

However, evidence about the effect of the level of prescribing outside hospital on the overall prevalence of resistant microbes is both limited and imprecise. A positive correlation between antibacterial prescribing in general practice and antibacterial resistance in coliform organisms in routine urine samples has been reported in Wales,[10] but a smaller study in the Wirral district of England could only partially replicate these findings and disputed the conclusions.[11] In countries with well developed systems of primary medical care, the extent to which a reduction in community based antibacterial prescribing will reduce antibacterial resistance has not been quantified. We conducted this study to try to replicate the positive correlation between prescribing and resistance[10] in a wider geographical area and range of pathogens, to estimate the effect of a reduction in community prescribing on antibacterial resistance in community pathogens, and to determine the usefulness of routine microbiological data for monitoring antibacterial resistance in the community.

Methods

We obtained the results of assessment of routine general practice microbiological specimens from seven Public Health Laboratory Service laboratories in the south and west of England (Gloucester, Bristol, Bath, Hereford, Plymouth, Reading, and Southampton) for 1 April 1997 to 31 March 1998. The same microbiological data were also obtained from 10 primary care groups (administrative areas usually consisting of 10-15 general practices) in the north west of England for 1 April 1996 to 31 March 1997. We did not seek approval from ethics committees.

We had data from 405 general practices. For each bacterial isolate, we obtained data on the general practice from which the specimen had been sent, the type of specimen, and the antibacterial susceptibilities reported. Repeat isolates with the same susceptibility pattern were excluded. We also had data on the total number of specimens received from each practice, except for practices in the north west.

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We obtained list sizes for practices from the Department of Health Prescribing Support Unit. List sizes were available quarterly from April 1996 to March 1998 for most practices, but for 43 practices estimates for 1997-8 were based on the first quarter only. We also obtained prescribing data for the practices from the Prescriptions Pricing Authority (PACT) database for the periods in which laboratory data were analysed. Practices with a registered list size of less than 500 were excluded as being too small to give useful information. We also excluded practices outside the normal catchment area of the participating laboratories. We ascertained the primary care group to which each practice belonged so that practice data could be aggregated into primary care groups. The 405 practices were from 38 primary care groups.

The analysis focused on organisms that cause the two most common indications for systemic antibacterial prescribing in UK general practice (urinary tract and respiratory tract infections) and the drugs most commonly used to treat these conditions. Resistance to these antibacterial drugs was examined in relation to urinary coliforms and isolates of *Streptococcus pneumoniae* from all sites.

For urinary tract infection, we examined resistance to ampicillin or amoxicillin and trimethoprim. We included data only from the 371 practices with 10 or more coliform isolates to increase statistical precision. The exact number of practices contributing to each analysis depended on the range of antibacterial drugs that the laboratory tested for susceptibility.

We plotted each practice's prescribing rate (prescriptions issued/1000 registered patients) of ampicillin or amoxicillin and of trimethoprim against the proportion of urinary coliform isolates resistant to the drug and calculated Spearman's rank correlation coefficient. Because resistance to ampicillin and amoxicillin can be due to production of β lactamase, the use of any β lactam antibacterial could potentially select for or induce this resistance. We therefore examined the association between ampicillin and amoxicillin resistance and prescribing of all β lactam antibacterials. In each case, we calculated the slope of the linear regression of resistance on prescribing, weighted by the number of bacterial isolates.

The rate at which specimens were sent for analysis varied greatly among practices (8-255/1000 patients/year) and showed weak negative correlations with resistance (significant only for trimethoprim; $r_s = -0.14$, $P = 0.02$). Rate of sending specimens was also positively correlated with prescribing of trimethoprim ($r_s = 0.21$, $P = 0.0001$) but not with prescribing of any other antibacterial drug. We therefore did multiple regression analyses with the rate of sending specimens as a covariate. However, the results were minimally different from the simple regression results and so we have presented the results of only the simple regression.

The same series of analyses were carried out with data aggregated to primary care group level, for the 32 groups for which data was available from at least four practices. We excluded six primary care groups for which data were available from only one or two practices to improve the representativeness of estimates of prescribing and resistance.

Few isolates of *S pneumoniae* were sent by each practice and antibacterial resistance is less common. We therefore divided practices into three groups (low, medium, and high prescribers), with cut-off points at the first and third quartile, according to the level of prescribing of each antibacterial drug. Once again, resistance to a drug could be selected for or induced by exposure to drugs with a similar action. We therefore assessed penicillin resistance against the prescribing of phenoxymethylpenicillin, all penicillins, and all β lactams, and erythromycin resistance against the prescribing of erythromycin and all macrolides.

We analysed the data using SAS version 6.12. Confidence intervals for the overall proportion of resistant isolates were adjusted for clustering by general practice.[12] We compared proportions using the χ^2 test and the test for linear trend.

Results

Urinary coliforms

Susceptibility to ampicillin or amoxicillin was determined for 29 585 isolates and to trimethoprim for 39 442 isolates. The proportion of urinary coliform isolates resistant to the most commonly used antibacterial drugs was high (ampicillin or amoxicillin 44.0% (13 022), 95% confidence interval 43.4% to 44.6%; trimethoprim 25.4% (10 029), 24.8% to 26.0%). Table 1 shows the correlation between antibacterial resistance and prescribing at practice and primary care group level. At practice level, low but significant correlations ($P < 0.01$) were evident between prescribing and resistance. At primary care group level, the estimated correlations were stronger ($r_s = 0.31$-0.57) but less significant because of the relatively small number of groups.

Table 2 gives the results of the regression analyses, and the figure shows the scatter plots for those that were significant. There is a wide degree of scatter, and the proportion of the variability in resistance "explained" by the regression was 6-16%. The mean annual practice prescribing rate of ampicillin and amoxicillin was 251/1000 patients. The regression predicts that a practice prescribing at 20% less than the mean rate would have 0.94 (95% confidence interval

Table 1 Correlation between antibacterial resistance of urinary coliforms and prescribing at primary care group and practice level

		Primary care group			Practice		
Antibacterial resistance*	Antibacterial prescribing†	No	r_s‡	P value	No	r_s‡	P value
Ampicillin or amoxicillin	All β lactams	20	0.57	0.009	262	0.18	0.003
	Ampicillin and amoxicillin	20	0.44	0.05	262	0.20	0.001
Trimethoprim	Trimethoprim	32	0.31	0.09	371	0.24	0.0001

*Resistant isolates per 100 isolates.
†Prescriptions per 1000 patients a year.
‡Spearman's correlation coefficient.

Table 2 Results of regression of antibacterial resistance of urinary coliforms on prescribing at primary care group and practice level

Antibacterial resistance*	Antibacterial prescribing†	Primary care group			Practice		
		No	Regression coefficient (95% CI)	Adjusted R^2‡	No	Regression coefficient (95% CI)	Adjusted R^2‡
Ampicillin or amoxicillin	All β lactams	20	0.012 (0.0004 to 0.023)	0.163	262	0.012 (0.007 to 0.018)	0.070
	Ampicillin and amoxicillin	20	0.013 (–0.003 to 0.029)	0.084	262	0.019 (0.011 to 0.026)	0.076
Trimethoprim	Trimethoprim	32	0.119 (–0.004 to 0.241)	0.092	371	0.078 (0.046 to 0.111)	0.057

*Resistant isolates per 100 isolates.
†Prescriptions per 1000 patients a year.
‡Shows the proportion of the variance in resistance "explained" by the regression.

0.02 to 1.85) fewer resistant isolates per 100 than the mean prescriber. The other significant regressions ($P < 0.05$) similarly predict that practices prescribing at 20% less than the mean will have about one less resistant isolate per 100 routine specimens containing urinary coliforms.

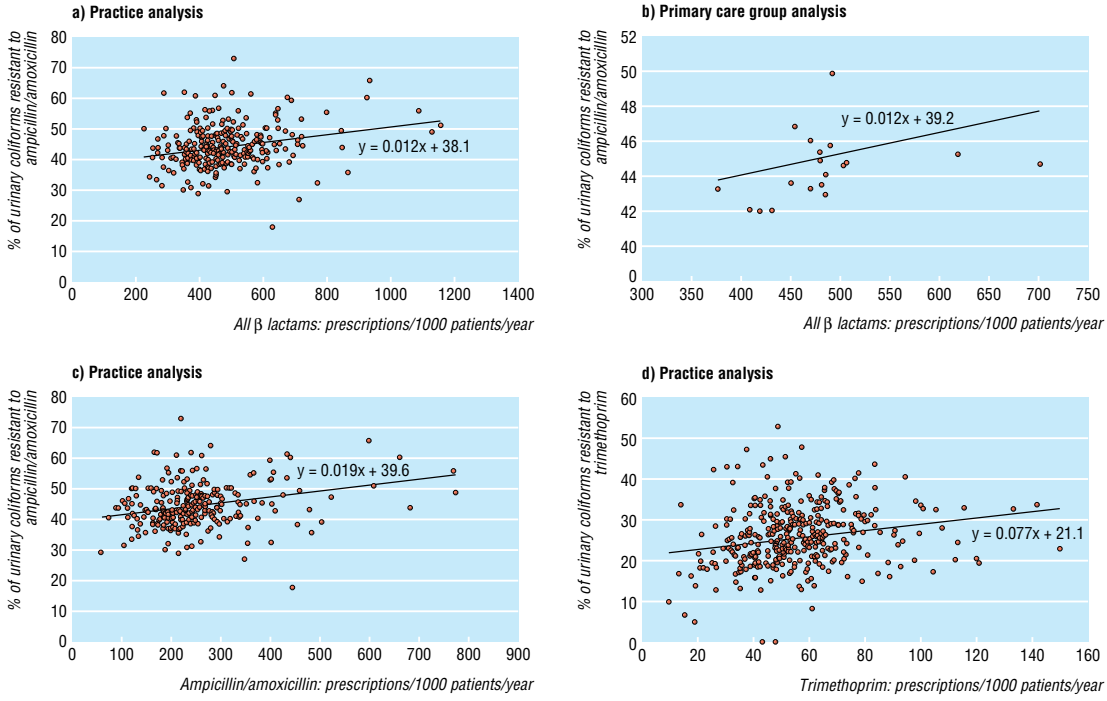
Pneumococci

Only 274 practices sent isolates of *S pneumoniae* for analysis. Susceptibility to penicillin was determined for 778 isolates from 260 practices and to erythromycin for 828 isolates from 257 practices. Table 3 shows the relation between antibacterial prescribing and resistance of pneumococci. Penicillin resistance was uncommon (2.2% (17), 95% confidence interval 1.2% to 3.2%), and there was no positive relation with prescribing of either penicillin or β lactams. Levels of resistance were higher for erythromycin (6.0% (50), 4.3% to 7.7%), and the proportion of resistant isolates tended to increase from the low to high prescribing groups, although the results were not significant. There were too few isolates to allow analysis at practice or primary care group level.

Discussion

Our findings are similar to those reported by Magee et al,[10] who showed that resistance to an antibacterial drug among routine urinary coliform isolates is correlated with community prescribing of that drug. However, the size of the correlation is modest, and our data suggest that practices with substantial differences in antibacterial use have only small absolute differences in resistance in routine specimens.

Prescribing explains at most 16% of the variation in resistance in these data. This must partly reflect the limitations of our methods, which relied on available data. Taking the overall number of prescriptions issued (and ignoring age, dose, and length of prescription) is a crude approach to measuring population exposure to antibacterial drugs. Also, transmission of pathogenic microbes will be determined by social interactions (at work, home, or school and when shopping or travelling, etc). These interactions do not respect practice boundaries, so practice prescribing is not a perfect measure of the antibacterial exposure of a community's pathogens. The fact that the correlations between prescribing and resist-



Relation between prescribing rate of antibacterial drugs and proportion of resistant urinary coliform isolates by individual general practice and (for all β lactams only) primary care group

Table 3 Proportion of pneumococci isolates resistant to antibacterial drugs in low, medium, and high prescribing practices*

Antibacterial resistance	Antibacterial prescribing	Proportion of resistant isolates (%)		
		Low prescribing	Medium prescribing	High prescribing
Penicillin	Phenoxymethylpenicillin	2/169 (1)	9/396 (2)	6/213 (3)
	All penicillins	6/186 (3)	8/390 (2)	3/202 (1)
	All β lactams	6/178 (3)	9/397 (2)	2/203 (1)
Erythromycin	Erythromycin†	7/164 (4)	24/441 (5)	19/223 (8)
	All macrolides‡	7/152 (5)	27/466 (6)	16/210 (8)

*Cut-off points between low and medium prescribing and medium and high prescribing practices were 42.4 and 72.9 for phenoxymethylpenicillin; 335.4 and 455.0 for all penicillins; 384.7 and 525.6 for all β lactams; 50.6 and 97.2 for erythromycin; 64.0 and 116.6 for macrolides.
†χ^2=3.60 (P=0.17), χ^2 for trend=3.27 (P=0.07).
‡χ^2=1.52 (P=0.47), χ^2 for trend=1.49 (P=0.22).

ance were stronger at primary care group level than at practice level emphasises the role of transmission in a geographically coherent population in determining the prevalence of resistance.

The use of routine specimens to measure resistance may also have contributed to the observed scatter and has the potential to introduce bias. Although practices sent specimens for analysis at widely varying rates, we were not able to detect confounding by rate of sending specimens. However, other factors that we could not measure may affect the cross sectional relation between prescribing and resistance. These include avoidance of antibacterial drugs to which resistance is known to be a local problem, the use of agricultural antibacterials in rural areas, and a time lag between prescribing and the rise in resistance (although an analysis (not shown) using the previous year's prescribing gave the same results).

Contribution of community prescribing to resistance

Magee et al's results were interpreted as supporting the view that community based prescribing is an important contributor to antibacterial resistance and that prescribing should therefore be reduced.[10] However, this is an oversimplification. The correlation coefficients are low, and the absolute difference in levels of antibacterial resistance between high and low prescribing practices is small. Mathematical modelling suggests that, where communities' prescribing and resistance is in equilibrium, the cross sectional relation between prescribing levels and resistance is an S shaped curve.[13]

In our data the slope of the relation was slight. If our practices represent communities in equilibrium, then the regressions predict that a practice that reduced prescribing by as much as 20% from the mean may see an absolute reduction in resistance of only 1% of routine urinary coliform isolates. This may be because there is no strong relation between overall prescribing and resistance in routine specimens or because the United Kingdom is currently on the initial (flat) part of the "S." The speed of any reduction in resistance depends on the starting level of prescribing but will be slower than the rise in resistance caused by using antibacterials.[13] Also, the effect of the levels of resistance that we found on clinical outcome is unknown. It could therefore be argued that reducing overall antibacterial prescribing in a well organised system of primary care (such as in the United Kingdom) does not deserve high priority for scarce government resources.

There may, however, be particular aspects of prescribing (for example, within hospitals or to particular age groups) that drive the overall prevalence of resistance in the community. These could be targeted as part of a more specific strategy, rather than simply trying to reduce overall levels of antibacterial prescribing. The feasibility of varying dose and length of treatment, and of minimising transmission in specific groups (toddlers in nurseries, elderly people in residential homes) should be investigated as potential strategies to limit or reduce antibacterial resistance in the community. We would not wish our findings to undermine any attempt to improve the quality of clinical care in general practice, including the more appropriate use of antimicrobial drugs.

Monitoring resistance

Arrangements to monitor antibacterial resistance in the community in the United Kingdom are still based on the use of routine data. Our study shows that this approach is crude, and the predicted small differences in resistance are unlikely to be detectable using routine sampling at the level of the individual practice or even primary care group. We therefore recommend establishing a new system of national surveillance based on systematic random sampling in selected practices, initially in patients who meet case definitions that put them at high risk of being infected with important pathogens. If these surveillance practices were chosen to represent socially and geographically coherent areas in terms of the factors likely to influence transmission, then such

What is already known on this topic

The probability of an individual hosting a resistant organism is increased by recent use of an antibacterial drug

Correlation between antibacterial prescribing and coliform resistance in routine microbiological samples from the community has been reported in one study

What this study adds

In English general practice, there are significant but low correlations between antibacterial prescribing and resistance in routine isolates of urinary coliforms

Substantial differences in prescribing between high and low prescribing practices are associated with only small differences in resistance

Improved methods of assessing national antimicrobial resistance are required

sampling would also facilitate better estimates of the relation between prescribing and important resistance in the community.

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Commentary: antibiotic resistance is a dynamic process

Richard Wise

Few would argue that natural selection is not one of the major and potent forces in nature. In medicine, one of the most dynamic examples is the interaction between bacteria and antimicrobial drugs. Some 60 years of use (a mere blink in evolutionary time) has generated resistance to many compounds in nearly all pathogens. What does the future hold? There are pessimists such as Steve Jones, who suggests that "bacteria are bound to win the war against medicine … Nowhere else does the evolutionary battle take place in an area where one player (the bacteria) holds all the cards … medicine's finest days may soon be over, but antibiotics, in their brief flowering, have revealed as can nothing else what evolution needs to do its finest work!"[1]

Many consider this view unduly pessimistic, and national strategies in Europe and North America are based on the belief that the process can be reversed (or at least held in check) by reducing the selection pressure—that is, using antibiotics more prudently. The paper by Priest et al adds to this debate, although differing conclusions could be drawn from it. For example, the minimal variation in ampicillin and trimethoprim resistance between practices with differing rates of prescribing (and various criteria for submitting specimens to a laboratory) does not necessarily imply that a change in prescribing would not affect resistance.

The dynamics of the interplay between prescribing and resistance are exceedingly complicated. Mathematical modelling gives some insights.[2] Generally, resistance rates are low after a new antimicrobial drug is introduced into a community; resistance then appears and increases steadily until it reaches a steady state level. (The rate of increase in resistance depends on the drug and how much is used, the bacteria, and the nature of the community—for example, the opportunity for cross infection.) If ampicillin and trimethoprim are at steady state level in the United Kingdom, we would expect little interpractice variation. Such models also predict that the decline in resistance after withdrawal of an antibiotic selection pressure will be uncomfortably slow.

Nevertheless, Priest et al make several important points. Firstly, although measuring resistance rates from routinely submitted laboratory samples may be inexpensive, it yields no denominator data. This means that any conclusions must, at best, be tentative. More meaningful bacterial susceptibility surveillance data are needed from selected groups, especially young and elderly people. Secondly, long term prescribing data linked to such resistance surveillance is prerequisite for drawing up national and local prescribing guidance.

In the United Kingdom, a public campaign has reduced antibacterial prescribing in general practice by 19%,[3] and a Belgian campaign has reduced prescribing for respiratory tract infection.[4] This must represent a move in the right direction, and until we have robust information to the contrary, judicious antibiotic use is the only path to follow.

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