

Age- and sex-specific antibiotic prescribing patterns in General Practice in England and Wales, 1994 to 1998

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In recent years, there have been several initiatives to encourage more prudent prescribing of antibiotics, particularly in primary care. Using information from 210 general practices in the General Practice Research Database with a total list size of 1.4 million patients, we examined trends in antibiotic prescribing in general practice in England and Wales between 1994 and 1998. The age-standardised antibiotic prescribing rate in 1998 was 575 per 1,000 in males and 800 per 1,000 in females. Antibiotics were prescribed most frequently to children and the elderly. There was a decline in the use of all antibiotics between 1994 and 1998, particularly among the more commonly used antibiotics and among children. Age-standardised prescribing rates were higher in the most deprived electoral wards and the rate of fall in prescribing was also lowest in these areas. There was a more than five-fold variation in prescribing rates among the 210 practices in this study, from 289 to 1,597 per 1,000 patients.

INTRODUCTION

The increase in antibiotic resistance is one of the most worrying trends facing 21st century medicine. Doctors worldwide have noted the ever-increasing prevalence of resistant organisms and the problems this is leading to. For example, there have been recent reports of deaths among children in the community in the USA attributed to antimicrobial resistance.¹ In the United Kingdom (UK), antibiotic resistance within hospitals is becoming an increasingly important problem. Much antibiotic prescribing is likely to be of limited therapeutic value and there is some evidence that lower rates of antibiotic prescribing may also lead to lower rates of antibiotic resistance.²

To help reduce antibiotic prescribing rates, doctors have been encouraged to prescribe more rationally and to follow evidence based guidelines when prescribing antibiotics.³ There is some evidence that national programs can have an effect on prescribing rates.^{4,5} In 1998, the Department of Health's Standing Medical Advisory Committee published a major report on antibiotic resistance.⁶ More recently, the Department of Health has established a Specialist Advisory Committee on Antimicrobial Resistance to take forwards work in this area. In the UK, general practitioners prescribe the majority of antibiotics and some of the key components of the strategy to reduce antibiotic prescribing are aimed at this group. However, there has been very little research examining recent trends in antibiotic prescribing in primary care.⁷

We analysed data from the General Practice Research Database (GPRD) to examine trends in antibiotic prescribing by general practitioners for the period 1994 to 1998. Our main objective was to examine whether guidelines on antibiotic prescribing, publication of research studies, and evidence from advisory bodies published from the mid 1990s onwards influenced the antibiotic prescribing practice of

general practitioners in England and Wales.^{3, 5, 8, 9} Because a reduction in the prescribing of antibiotics could lead to a lower prevalence of bacterial resistance,¹⁰ our findings may have important implications for both the NHS and for other health care systems.

We used recent data from the GPRD to examine the age- and sex-specific prescribing rates for the main antibiotic groups between 1994 and 1998; the trends in overall antibiotic prescribing; to assess the percentage of each age group prescribed an antibiotic in each year; and to examine the variation in antibiotic prescribing rates between general practices, NHS regions, and between deprived and affluent areas. We also looked in more detail at the use of the quinolones, a group of antibiotics that are felt to be less appropriate as first line treatment in primary care.

METHODS

The antibiotic prescription data used in this study came from 210 general practices in England and Wales contributing data to the General Practice Research Database (GPRD). The total list size was 1.4 million patients in 1998, representing 2.6 per cent of the population of England and Wales. There is some variation in coverage between regions from 1.4 per cent in North Thames to 3.4 per cent in West Midlands. The GPRD was originally set up in 1987 by the VAMP software company and was acquired by Reuters Health Information Ltd. who in 1994 donated it to the Department of Health. The Office for National Statistics (formerly OPCS) operated the database from 1994 to 1999. The Medicines Control Agency has been responsible for the overall management and financial control of GPRD since April 1999, and its operation since October 1999.

Participating practices follow agreed guidelines for the recording of clinical and prescribing data and submit anonymised, patient-based clinical records on a regular basis to the database. All of the 210 practices included in this analysis contributed data throughout the five-year period 1994 to 1998 that passed regular quality checks. The accuracy and comprehensiveness of the data recorded in the GPRD has been documented previously.^{11, 12, 13, 14} The combined population of the practices in 1998 had a very similar age-sex composition to the mid-1998 population of England and Wales.¹⁵ Prescribing information is recorded using either VAMP or Multilex drug codes. These codes are mapped to the classification used by the British National Formulary (BNF). Prescribing information can be extracted using these mappings.

Antibiotic prescriptions

All prescription items for antibacterial drugs (BNF section 5.1) issued during the year were included in the analysis and were classified by type of antibiotic. Only prescriptions issued while patients were registered and therefore 'at risk' were included. The data relate to prescriptions issued and recorded by GPs and not to prescriptions dispensed.

For the most recent years for which prescribing data were available (1994 to 1998), we calculated age- and sex-specific prescribing rates for selected antibiotic categories, based on British National Formulary definitions. To allow direct comparison of the rates over time, between the sexes, and across regions and deprivation categories, directly age-standardised rates were calculated (based on the European Standard Population). The percentage of patients in each age-sex group receiving at least one prescription for an antibiotic was also calculated. Finally, we examined the overall variation in antibiotic prescribing rates among the 210 practices. Prescribing rates for 1998 are presented along with some trend data for 1994 to 1998.

As not all patients were registered with the practices for the entire duration of the study, prescribing rates were calculated as the number of prescriptions per 1,000 patient years at risk. Patient years at risk were calculated as the sum of the number of days that patients were registered during the year, divided by the number of days in the year.

Geographic and area deprivation classifications

In the GPRD, no information is available on where the practice patients live so all geographic and socio-economic analyses are based on practice location. Practice postcode is used to ascertain which electoral ward the practice is located in. Data were aggregated for all participating practices in each region and deprivation category. The analysis of regional variation in antibiotic prescribing patterns used *NHS Regional Office areas* for England, which dated from April 1996 (when they replaced Regional Health Authorities) and comprised eight areas.

The deprivation categories used in the study are derived using the Townsend Material Deprivation Score.¹⁶ This is a composite score calculated using information on unemployment, overcrowding, car availability and home ownership derived from 1991 Census data; the percentage of: i) economically active residents aged 16–59/64 who are unemployed, ii) private households with more than one person per room, iii) private households with no car and iv) private households not owner occupied. The higher the score the greater was the level of relative deprivation in 1991.

The Townsend Scores for all wards in England and Wales were arranged in ascending order of Townsend Score along with the total population of each ward in 1991. The wards were divided into five groups each of which contained 20 per cent of the total population of England and Wales. A range of Townsend Scores describes each of these population quintiles. Each general practice was allocated to a quintile on the basis of the Townsend Score of the ward in which it is located. There was one practice for which it was not possible to obtain ward information. Consequently data for this practice are not included in the deprivation analysis.

RESULTS

Age- and sex-specific prescribing rates of antibiotics

The age-standardised antibiotic prescribing rate in 1998 was 575 per 1,000 in males and 800 per 1,000 in females (Table 1). Broad-spectrum penicillins were by far the most commonly prescribed antibiotics in both sexes, and accounted for 40 per cent of all antibiotic prescriptions. In children aged under five years, broad-spectrum penicillins accounted for about 60 per cent of antibiotics prescribed.

In males and females there was a U-shaped relationship between antibiotic prescribing rates and age, although this association was less marked in women. Rates of metronidazole and tinidazole prescribing were higher in women aged 16 to 44 years, probably representing treatment of gynaecological infections. Sulphonamides and trimethoprim were more frequently prescribed to women, with rates highest in elderly women. This is probably due to treatment of urinary tract infections. Tetracyclines were most commonly prescribed to men aged 16 to 24, probably reflecting their use in the treatment of acne.

Prescribing rates between 1994 and 1998

Prescribing rates of most antibiotic groups peaked in 1995 and then decreased (Table 2). Overall, antibiotic prescribing rates decreased by nine per cent in males and eight per cent in females between 1994 and 1998. The decrease between 1995 and 1998 is even more striking (18

per cent in males and 16 per cent in females). There were some exceptions to this; for example, the use of penicillinase-resistant penicillins appears to be increasing. The reduction in prescribing rate is most marked in the antibiotic classes prescribed most frequently. The rate of quinolone prescribing has remained fairly constant, as have the rates of prescribing of metronidazole and tinidazoles.

Total antibiotic prescription items by age, sex and calendar year

There has been a marked reduction in antibiotic prescribing in both sexes and in most age groups between 1994 and 1998 (Table 3). The decrease is greatest in young children, with a reduction of 17 per cent in children under five years. During the period 1995 to 1998, there were

even more striking reductions in antibiotic prescribing rates, again most marked among children. In women aged over 74 years, however, antibiotic prescribing rates increased between 1994 and 1998.

Variation by NHS region and area deprivation

During the period 1994 to 1998, the age-standardised antibiotic prescribing rate was constantly around one third higher in Wales and in the northern regions (Northern & Yorkshire and North West NHS regions), compared to the southern regions (South Thames, and South and West) (Table 4). During the same period, there were also large differences in age-standardised antibiotic prescribing rates by area deprivation (Table 5). The rates were consistently highest among patients registered with practices located in the most deprived fifth of

Table 1 Age-specific prescribing rates of antibiotics per 1,000 patients, 1998

BNF* Section Antibiotic	Age										Crude rate (all ages)	Age-standardised rate (all ages)*	Number of prescriptions
	0-4	5-15	16-24	25-34	35-44	45-54	55-64	65-74	75-84	85 and over			
Males													
5.1.1.1. Benzylpenicillin & phenoxymethylpenicillin	92	86	73	42	31	21	20	20	17	15	45	47	27,400
5.1.1.2. Penicillinase-resistant penicillins	61	49	46	35	37	34	40	48	60	87	43	44	26,525
5.1.1.3. Broad-spectrum penicillins	850	298	138	130	147	159	211	286	345	398	236	249	144,921
5.1.2. Cephalosporins, cephamycins etc.	122	43	23	21	24	30	46	73	101	133	43	44	26,663
5.1.3. Tetracyclines	0	20	154	51	44	49	60	77	69	48	57	57	34,978
5.1.5. Macrolides	216	89	80	48	49	47	63	80	89	88	73	77	45,078
5.1.8. Sulphonamides & trimethoprim	69	17	13	13	16	19	33	53	82	131	28	28	16,922
5.1.11. Metronidazole & tinidazole	1	1	4	6	7	8	11	14	12	12	7	6	4,180
5.1.12. Quinolones	0	1	7	11	14	18	26	43	59	73	17	15	10,287
5.1.13. Treatments for urinary-tract infections	1	0	1	1	1	2	2	6	7	14	2	2	1,144
Other antibiotics in 5.1	3	3	4	3	4	5	9	12	12	8			
5.1. Total antibiotic prescriptions	1,418	609	541	361	374	393	521	712	854	1,007	556	575	341,504
Females													
5.1.1.1. Benzylpenicillin & phenoxymethylpenicillin	81	121	126	84	53	34	30	25	20	19	66	71	41,359
5.1.1.2. Penicillinase-resistant penicillins	49	52	52	48	43	42	41	51	66	96	50	48	31,268
5.1.1.3. Broad-spectrum penicillins	764	323	236	259	243	243	290	303	309	351	300	310	188,841
5.1.2. Cephalosporins, cephamycins etc.	116	60	68	75	70	75	94	117	140	160	86	82	53,919
5.1.3. Tetracyclines	0	19	101	69	76	78	70	61	46	28	61	60	38,192
5.1.5. Macrolides	176	100	103	92	88	81	91	95	88	86	96	99	60,560
5.1.8. Sulphonamides & trimethoprim	76	43	73	66	69	74	89	108	146	190	80	75	50,532
5.1.11. Metronidazole & tinidazole	2	3	33	41	29	19	17	18	15	21	22	21	13,560
5.1.12. Quinolones	1	2	12	18	23	30	37	48	53	58	24	21	15,310
5.1.13. Treatments for urinary-tract infections	1	2	6	7	7	7	12	16	23	29	9	7	5,540
Other antibiotics in 5.1	4	3	4	3	4	5	7	11	8	4			
5.1. Total antibiotic prescriptions	1,270	729	814	761	706	689	778	852	914	1,042	798	800	502,263

* Direct age-standardisation using the European standard population.

+ British National Formulary.

Table 2 Age-standardised prescribing rates per 1,000 patients for antibiotic groups*, 1994 to 1998

BNF* Section Antibiotic	Males					Females				
	1994	1995	1996	1997	1998	1994	1995	1996	1997	1998
5.1.1.1. Benzylpenicillin & phenoxymethylpenicillin	62	63	59	54	47	94	94	88	82	71
5.1.1.2. Penicillinase-resistant penicillins	33	36	38	42	44	37	39	42	48	48
5.1.1.3. Broad-spectrum penicillins	277	316	294	291	249	343	390	361	361	310
5.1.2. Cephalosporins, cephamycins etc.	50	54	53	52	44	83	92	90	91	82
5.1.3. Tetracyclines	68	69	62	60	57	73	75	69	66	60
5.1.5. Macrolides	80	98	87	87	77	100	120	110	111	99
5.1.8. Sulphonamides & trimethoprim	38	33	30	29	28	89	83	78	78	75
5.1.11. Metronidazole & tinidazole	5	6	7	6	6	22	21	21	21	21
5.1.12. Quinolones	14	15	16	16	15	21	21	22	22	21
5.1.13. Treatments for urinary-tract infections	2	2	2	2	2	7	8	8	8	7
5.1. Total antibiotic prescriptions	633	697	653	646	575	869	948	892	894	800

* Direct age-standardisation using the European standard population.

+ British National Formulary.

Table 3 Total antibiotic prescriptions per 1,000 patients, by age, sex and calendar year, 1994 to 1998

	Age										Crude rate (all ages)	Age-standardised rate (all ages)*
	0-4	5-15	16-24	25-34	35-44	45-54	55-64	65-74	75-84	85 and over		
Males												
1994	1,700	715	552	387	405	408	536	739	915	1,053	614	633
1995	1,812	824	637	438	444	452	576	786	942	1,124	675	697
1996	1,734	703	598	404	413	428	582	769	929	1,083	631	653
1997	1,671	715	574	406	419	433	572	767	940	1,017	624	646
1998	1,418	609	541	361	374	393	521	712	854	1,007	556	575
% change 1994-98	-16.6	-14.8	-1.9	-6.9	-7.5	-3.7	-2.7	-3.6	-6.7	-4.4	-9.5	-9.2
% change 1995-98	-21.8	-26.1	-15.1	-17.7	-15.8	-13.1	-9.5	-9.4	-9.3	-10.4	-17.6	-17.5
Females												
1994	1,538	835	856	815	772	735	800	855	882	1,014	861	869
1995	1,639	949	966	900	831	782	867	905	911	1,058	933	948
1996	1,549	831	899	843	781	754	844	893	934	1,069	882	892
1997	1,507	836	902	846	794	756	855	904	956	1,073	886	894
1998	1,270	729	814	761	706	689	778	852	914	1,042	798	800
% change 1994-98	-17.4	-12.8	-4.9	-6.5	-8.5	-6.3	-2.7	-0.3	3.6	2.8	-7.3	-8.0
% change 1995-98	-22.5	-23.2	-15.8	-15.4	-15.0	-11.9	-10.3	-5.9	0.3	-1.5	-14.5	-15.6

*Direct age-standardisation using the European standard population.

Table 4 Total antibiotic prescriptions per 1,000 patients, by NHS region (April 1996 boundaries) age-standardised rates,* 1994 to 1998

	Males					Females				
	1994	1995	1996	1997	1998	1994	1995	1996	1997	1998
NHS Region										
Wales	751	848	776	765	650	1,012	1,140	1,044	1,038	896
Northern & Yorkshire	694	773	715	727	653	963	1,062	1,000	1,020	921
Trent	607	666	623	634	561	835	906	863	901	793
Anglia & Oxford	617	657	603	599	570	845	903	835	860	806
North Thames	571	635	604	599	532	755	836	796	787	727
South Thames	556	612	581	554	481	762	841	805	757	671
South and West	566	604	569	562	493	776	835	778	775	683
West Midlands	657	721	679	653	581	899	974	928	917	805
North West	679	775	737	726	649	953	1,050	991	990	897

*Direct age-standardisation using the European standard population.

Table 5 Total antibiotic prescriptions per 1,000 patients, by area deprivation, age-standardised rates,* 1994 to 1998

	Males					Females				
	1994	1995	1996	1997	1998	1994	1995	1996	1997	1998
Deprivation Quintile										
Q1 (least deprived)	623	664	622	611	565	837	868	814	814	745
Q2	632	683	633	624	549	849	918	870	860	766
Q3	612	677	626	629	565	844	919	856	875	792
Q4	615	684	644	630	542	847	932	881	873	760
Q5 (most deprived)	682	767	732	722	650	967	1,080	1,018	1,021	921

*Direct age-standardisation using the European standard population.

electoral wards. In 1998, the rate in quintile five (most deprived) was 650 prescriptions per 1,000 patient years at risk among males and 921 among females, 15 and 24 per cent higher respectively compared to the rate in quintile one (least deprived). Between 1994 and 1998, the rate declined in all quintiles, but the decline was smallest for practices located in the most deprived areas.

Percentage of patients receiving an antibiotic in 1998

About half of all children under 5 years (52 per cent for boys and 49 per cent for girls) received an antibiotic prescription in 1998 (Figure 1). Except in children less than 5 years, more females received an antibiotic prescription in 1998 and overall, females were about 35 per cent more likely to be prescribed an antibiotic than men. In both sexes but more marked in males, there was a U-shaped relationship between age and the probability of receiving an antibiotic prescription.

Inter-practice variation in antibiotic prescribing rates

The prescribing rates for the 210 practices in this study varied nearly six-fold in 1998, from 289 to 1,597 per 1,000 patients, with a median rate of 660 per 1,000 and an inter-quartile range of 549 to 823 (Figure 2). There also appeared to be no correlation between total prescribing rates and prescribing of quinolones (Figure 3).

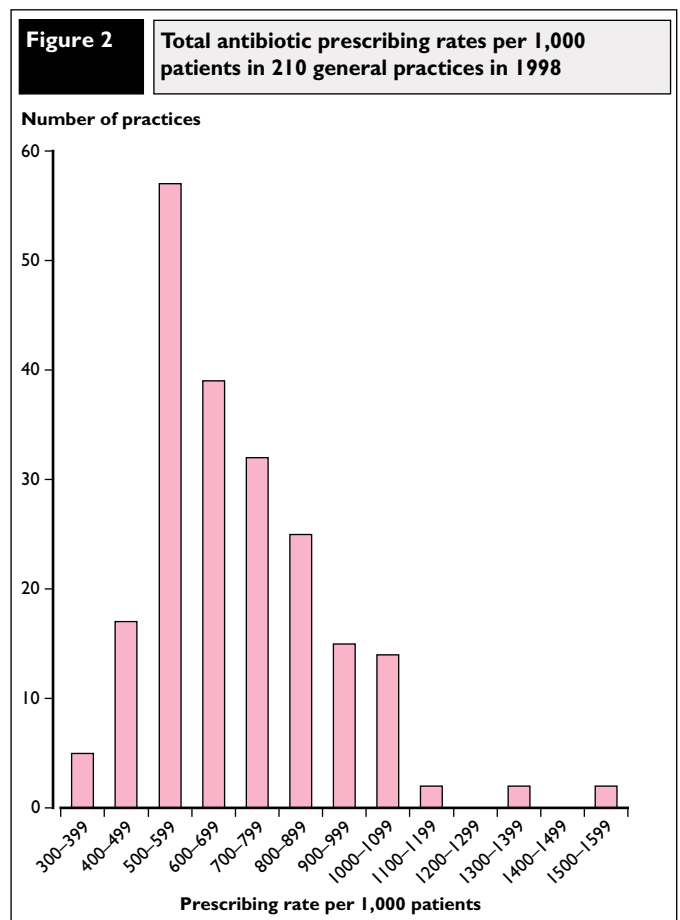
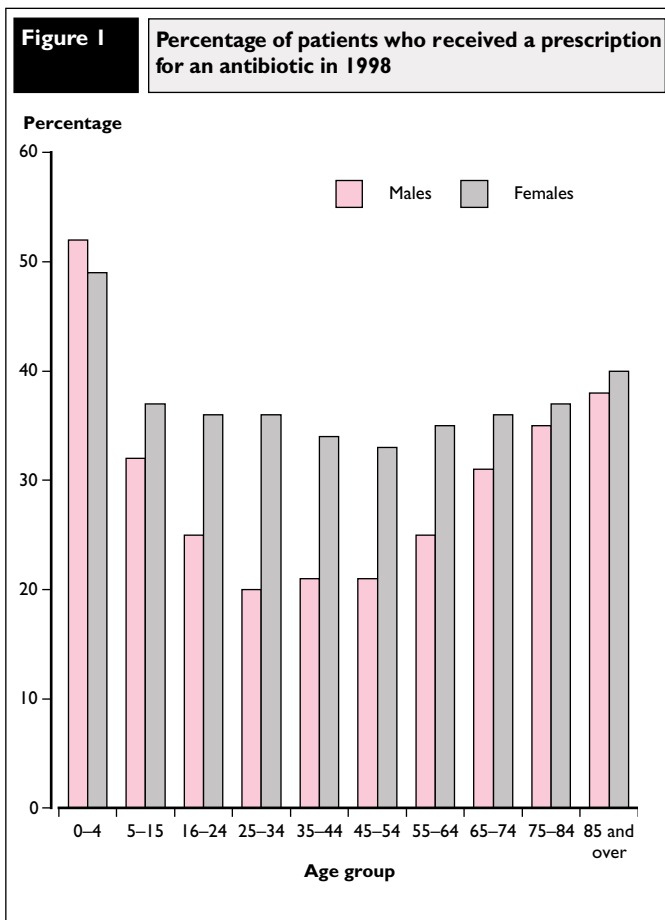
DISCUSSION

The most striking finding from this study is that antibiotic prescribing rates have fallen substantially since 1995. The decline in antibiotic prescribing rates began before the start of the Department of Health's drive in 1998 to reduce antibiotic prescribing. This suggests that

general practitioners were already aware of the need to reduce antibiotic prescribing and the limited effectiveness of antibiotics for many common community infections, and had begun to change their prescribing practice to reflect this. Whether this decline in antibiotic prescribing rates will translate into lower levels of antibiotic resistance in the community is unclear.^{17,18} However, the decline will have a number of other public health benefits, including lower NHS expenditure on antibiotics and a reduction in the rate of adverse reactions to antibiotics in the population. The study also shows that the likelihood of receiving an antibiotic prescription increases at the extremes of age. Except among young children, females are more likely to be prescribed an antibiotic at all ages.

Antibiotic prescribing rates were consistently higher in Wales and in northern England. Prescribing rates were also higher in practices located in the most deprived areas. There was also a marked variation in prescribing rates among the general practices in the study, with some practices prescribing less than 300 scripts per 1,000 patients compared to nearly 1,600 scripts per 1,000 at the other extreme. This variation is probably too large to be accounted for by differences in rates of infectious diseases and probably reflects differences in doctors' prescribing practices.

Antibiotic prescribing rates have fallen by about 17 per cent among 0- to 4-year-olds since 1994. From 1995 onwards (when antibiotic prescribing rates peaked), rates have fallen by about 22 per cent in this group. Hence, studies showing the limited value of antibiotics for conditions such as otitis media and upper respiratory tract infections, both of which are common in children, appear to be beginning to influence clinical practice. In line with recommended practice, most prescriptions in young children were for broad-spectrum penicillins and macrolides.¹⁹ The prescribing rate for boys under five years was higher than that in girls of the same age. The explanations for this difference are unclear.



Among 16- to 74-year-olds, women were much more likely to be prescribed an antibiotic than men. Much of this variation is in the use of broad-spectrum penicillins, cephalosporins, sulphonamides and trimethoprim. This difference is probably due to the use of antibiotics in the treatment of urinary tract and gynaecological infections. Because we were not able to examine the length of treatment, we were unable to assess the impact of guidelines for the treatment of uncomplicated urinary tract infections. These guidelines suggest limiting treatment of these infections to three days.^{4,20} Additional guidelines for health professionals on the treatment of gynaecological and genito-urinary infections may further help to rationalise antibiotic prescribing for women.

Antibiotic prescribing rates decreased less among the elderly than in other age groups, and among women aged over 74 years, prescribing rates increased between 1994 and 1998. Much of the research on the limited effectiveness of antibiotics has been for disorders such as otitis media and sore throat, which are commonest in children. Hence, most current guidelines are aimed at the treatment of children and there are few guidelines available for antibiotic prescribing in the elderly. If prescribing rates are to be reduced among the elderly, then evidence-based guidelines also need to be produced for this group. Because bacterial infections are often more serious in the elderly, general practitioners may be reluctant to change their prescribing practice in this group until better evidence is available.

There remain marked differences in prescribing rates between different regions, different practices located in areas of different socio-economic status, and between practices. All primary care trusts and general practices have access to Prescribing Analysis and Cost (PACT) data that can be used to provide detailed information on their prescribing rates and help influence prescribing. Questions that prescribing advisers and general practitioners can then ask include: What are the reasons for prescribing differences at a local level? Are the higher prescribing doctors less aware of prescribing guidelines? Would educational

interventions or prescribing incentive schemes help to reduce these differences? There is also evidence suggesting that parent and patient education can influence antibiotic use.²¹ This is also an area that primary care trusts and general practitioners may need to examine.

The rate of prescribing of quinolones remained fairly constant over the period of the study, but there remains a large variation in their use between practices. There was little association between the rates of quinolone prescribing and the overall antibiotic prescription rate. This suggests that the factors influencing antibiotic prescribing are complex and that those prescribing large amounts of antibiotics may be favouring certain antibiotic groups. Therefore guidelines aimed at reducing overall prescribing rates may by themselves not lead to better prescribing practice in the choice of antibiotic used.

STRENGTHS AND WEAKNESSES OF STUDY

The use of a delayed or reserve prescription, suggested as a method of reducing antibiotic use,¹⁹ would not be identified by this study. This may result in the prescribing rates in this study slightly over-estimating the number of prescriptions that patients actually have dispensed. However, Prescription Cost Analysis data for England (based on prescriptions dispensed) for the period 1991 to 2000 also show a large decrease (25 per cent) in the number of antibiotic prescriptions dispensed in the community since 1995 (Table 6).

We were unable to examine the average or median length of the prescriptions issued. If changes in antibiotic prescribing rates were due to prescribing guidelines, then it would be interesting to see if prescriptions are also for recommended strengths and lengths. A link between diagnosis and the antibiotic prescribed would also be useful, as this would allow analysis of trends in antibiotic prescribing for specific disorders.

CONCLUSIONS

General practitioners have reduced their antibiotic prescribing rates substantially since 1995. However, there remain marked differences in prescribing rates between general practices and in different parts of the country. There are also wide variations in antibiotic prescribing rates between different countries.²² There are a number of possible explanations for these variations. General practitioners' workload has increased in recent years and may be higher in some practices than in others. Many patients may still expect an antibiotic prescription when they present with an infection to their doctor. There may be differences in patient education levels. Some patients and doctors may still not perceive antibiotic resistance to be a problem that they can influence.²³ There is evidence that educational initiatives and feedback of data can

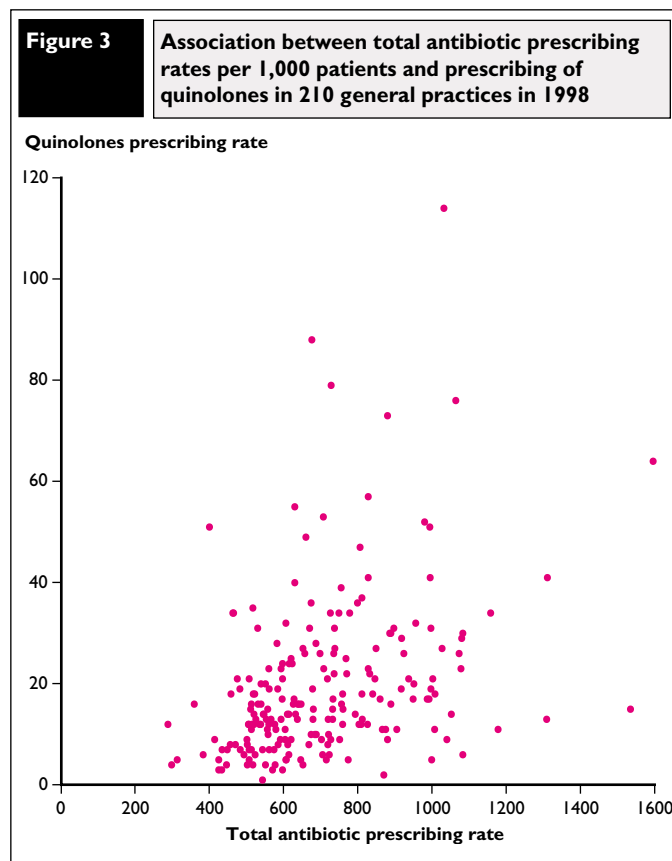


Table 6 Number of antibiotic prescriptions dispensed in the community in England, 1991 to 2000

Year	Prescription items (millions)	Net ingredient cost (£ millions)
1991	43.7	167.1
1992	43.4	170.4
1993	47.7	179.1
1994	45.8	177.5
1995	49.4	192.4
1996	46.6	174.4
1997	46.4	172.0
1998	42.6	163.0
1999	38.6	177.1
2000	36.9	172.2

Source: Department of Health's Prescription Cost Analysis for England.

influence prescribing rates. Hence, it is important that information and advice on the importance of reducing antibiotic prescribing continues to be disseminated.^{3,24}

A similar analysis to that carried out in this paper is not currently possible for hospital prescribing because there is no readily available source of data to do this. This is paradoxical, as the problem of antibiotic resistance is greatest in hospitals. This deficiency needs to be addressed to give a better overall picture of antibiotic prescribing and also to determine the effects of educational initiatives and guidelines on hospital doctors' antibiotic prescribing practice.

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Key findings

- The age-standardised antibiotic prescribing rate in England and Wales in 1998 was 575 per 1,000 in males and 800 per 1,000 in females.
- Antibiotic were prescribed most frequently to children and the elderly.
- There was a decline in the use of antibiotic between 1994 and 1998, particularly among children.
- Age-standardised prescribing rates were highest in the most deprived electoral wards and the rate of fall in prescribing was also lowest in these areas.
- There was more than five-fold variation in prescribing rates among the 210 practices in this study, from 289 to 1,597 per 1,000 patients.

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