

IN BRIEF

- Describes an audit undertaken in the East of England on antibiotic prescribing in general dental practice.
- The protocols of an original North West of England audit published in 2001 were deliberately replicated, in order to be able to pool the data and obtain a sample size of at least 1% of all UK dentists.
- The combined Regional results confirm that clinical audit reduces both the number of errors made by dental practitioners when writing out a prescription, as well as the number of those which are issued inappropriately, as compared to contemporary prescribing guidelines.

The impact of clinical audit on antibiotic prescribing in general dental practice

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Objective To reduce the number of antibiotics inappropriately prescribed by general dental practitioners, and to increase overall prescription accuracy. **Design** A prospective clinical audit carried out between September and March of 2002–3 and 2003–4. **Setting** General dental practices in Eastern England. **Subjects and methods** The pre-audit antibiotic prescribing practices of 212 general dental practitioners were recorded over an initial six week period. On each occasion this included which antibiotic had been chosen, together with its dose, frequency and duration, as well as the clinical condition and reason for which the prescription had been raised. When related to prophylaxis, the patient's medical history was also noted. Following education on contemporary prescribing guidelines, presentations which illustrated the practitioners' previous errors, and the agreement of standards to be achieved, the process was repeated for another six weeks, and the results compared. **Results** In the pre-audit period, 2,951 antibiotic prescriptions were issued, and during the audit this was reduced by 43.6% to 1,665. The majority were for therapeutic reasons, with only 10.5% and 13.6% for medical prophylaxis during the pre-audit and audit periods respectively. Over both periods, amoxicillin and metronidazole were the two most commonly prescribed antimicrobials (63.4% and 21.2% respectively). In the pre-audit period, only 43% of all prescriptions were error free in dose, frequency, and/or duration of use, but this rose significantly to 78% during the audit. Equally, using contemporary published guidelines, out of all the prescriptions made in the pre-audit period, only 29.2% were deemed to be justified, as compared to 48.5% during the audit. **Conclusions** Clinical audit, in conjunction with education, and prescribing guidelines can favourably change antibiotic prescribing patterns among general dental practitioners.

INTRODUCTION

More antibiotics are prescribed by general medical practitioners for patients who present to them with a tooth related problem than by either hospital or general practice based dentists,¹

and differences in prescribing practice between doctors and dentists for these patients also exist.^{1,2} Nevertheless, out of the 40 million oral antibiotics dispensed in the community in England each year, about 7% of them are prescribed by dentists.³ Throughout the United Kingdom, many have been shown to be both inappropriate and suboptimal,^{4–7} quite often given either as a substitute for operative intervention of a dental infection,⁷ or as an adjunct, even in the absence of any signs of systemic involvement.⁴ Such practice is not without its attendant consequences, which include life threatening anaphylactic reactions to penicillin with an estimated incidence of 0.04%,⁸ and the develop-

ment of potentially fatal orofacial infections.⁹ In addition, the destruction of a patient's commensal flora which occurs with a prolonged course of antibiotics, together with the associated abolishment of their colonisation resistance to pathogens then allows for selection and overgrowth of resistant 'super-bug' organisms.^{10,11} One such microbe is methicillin resistant *Staphylococcus aureus* (MRSA), hitherto a nosocomial (hospital acquired) infection, which on occasion has had an impact on post operative maxillofacial procedures.¹² However, evidence now exists that oral carriage of *S. aureus* is becoming more common, with this organism being isolated in a fifth of oral cavity specimens, of which 5%

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Table 1 The number of antibiotics that were prescribed by the GDPs during the pre-audit period, including the number which either had or did not have one or more errors in the prescription, together with the percentage of occasions when they were issued

Antibiotics prescribed in the pre-audit period	Number where the dose, frequency, and duration were all correct	Number where either the dose, frequency and/or duration were incorrect	Percentage of occasions when prescribed
Amoxicillin	878	1,004	63.8%
Metronidazole	135	453	19.9%
Erythromycin	94	79	5.9%
Penicillin V	55	68	4.2%
Clindamycin	50	19	2.3%
Amoxicillin & Metronidazole	20	48	2.3%
Others	36	12	1.6%
Totals	1,268	1,683	100%

Table 2 The number of antibiotics that were prescribed by the GDPs during the audit period, including the number which either had or did not have one or more errors in the prescription, together with the percentage of occasions when they were issued

Antibiotics prescribed in the audit period	Number where the dose, frequency, and duration were all correct	Number where either the dose, frequency and/or duration were incorrect	Percentage of occasions when prescribed
Amoxicillin	844	199	62.6%
Metronidazole	283	106	23.4%
Erythromycin	59	19	4.7%
Penicillin V	26	10	2.2%
Clindamycin	49	11	3.6%
Amoxicillin & Metronidazole	30	13	2.6%
Others	9	7	0.9%
Totals	1,300	365	100%

Table 3 The number and percentage of antibiotics which were prescribed by the GDPs in the pre-audit period, either appropriately or inappropriately, as determined by the FGDP RCS Eng Adult Antimicrobial Prescribing Guidelines, including in each division the number which either had or did not have one or more errors in the prescription

Antibiotics prescribed in the pre-audit period			
Appropriate		Inappropriate	
Prescription errors	Error free prescriptions	Prescription errors	Error free prescriptions
368	493	1,315	775
861 (29.2%)		2,090 (70.8%)	

Table 4 The number and percentage of antibiotics which were prescribed by the GDPs in the audit period, either appropriately or inappropriately, as determined by the FGDP RCS Eng Adult Antimicrobial Prescribing Guidelines, including in each division the number which either had or did not have one or more errors in the prescription

Antibiotics prescribed in the audit period			
Appropriate		Inappropriate	
Prescription errors	Error free prescriptions	Prescription errors	Error free prescriptions
135	672	230	628
807 (48.5%)		858 (51.5%)	

are of its resistant MRSA strain. These are more commonly recovered from samples taken from patients in primary care settings, such as nursing homes, hospices and general dental practices, and as such, oral carriage of MRSA may serve as a reservoir for re-colonisation of other body sites or for cross infection to other patients or health care workers.

However, it remains unclear whether the recovery of *S. aureus* oral isolates signifies an infective role, or merely one of colonisation.¹³

Nevertheless, at least two cases have been reported of cross infection from a general dental practitioner's un-gloved fingers to his patients, where the practitioner most probably had become colonised as a consequence of being hospitalised a year previously.¹⁴

To counter the general problem of the emergence of antibiotic resistant bacteria, the Standing Medical Advisory Committee's sub-group on antimicrobial resistance has recommended the development of high quality evidence-based prescribing guidelines, medical and dental education, campaigns of public education, and surveillance of success through national, regional and local audits.³

The dental profession's response so far has included one local audit in Aberdeenshire,¹⁵ and more recently a regional audit in the North West of England.¹⁶ The structure of the latter audit was found to be easily understood by 90% of the participants, and 69% of them felt the process had favourably changed their antibiotic prescribing practices.¹⁷

Therefore, the aim of this study was to replicate the North West of England regional audit, and to evaluate its effectiveness amongst general dental practitioners in Eastern England.

METHOD

Subject recruitment

At an annual meeting of postgraduate dental tutors of the Eastern Deanery in 2001, the possibility of running a clinical audit on antibiotic prescribing practices was discussed, along similar lines to the previously published North West of England study. Eight tutors volunteered to participate, through which ultimately a total of 212 dental practitioners from the counties of Bedfordshire, Hertfordshire, Essex, Norfolk, Suffolk and Cambridge were recruited.

Data collection

Copies of the *pro forma* which had been used in the North West of England study were used to collect information anonymously on each occasion an antibiotic was prescribed by a dentist in the Eastern Deanery. This included the antibiotic prescribed, its dose, frequency, and duration, the clinical condition and reasons for prescribing, as well as the patient's medical history (if a prescription was being made for medical prophylaxis).

Procedure

Before the start of the study, meetings were convened between the dental tutors and their local participating dentists to discuss the nature of the audit, to instruct on the use of the *pro forma*, and to agree on a commencement date for the project, which would result in the project both starting and finishing between the autumn and spring periods of the year in question. This restriction was imposed to avoid any possible prescribing variations that might exist between the warmer and colder seasons. In addition, an audit facilitator explained how each practitioner should ultimately complete their own individual audit report, and subsequently claim for reimbursement. Of the eight participating postgraduate dental tutors, five ran the exercise between the autumn and spring of 2002/2003, and three between 2003/2004.

Each study began with an initial six week period of data collection, primarily designed to establish and record existing antibiotic prescribing practices, with the *pro forma* returns being sent to the local dental tutors. The adult prescriptions were then analysed and assessed by the tutors using the Faculty of General Dental Practitioners (UK), Royal College of Surgeons of England guidelines on adult antimicrobial prescribing in primary dental care,¹⁸ while those which had been made for children were assessed using the British National Formulary.

At the end of this pre-audit period, the dentists reconvened at their respective postgraduate medical centres, in order to discuss the results of the data. They were informed of the collective areas of inappropriate and inaccurate prescribing by the dental tutors, and then received education from local consultants in microbiology and oral and maxillofacial surgery on the principles of appropriate

Table 5 The clinical conditions and the number of antibiotic prescriptions issued by the GDPs before and during the audit, showing the percentage change in the number of prescriptions between the two periods, for both the East of England, and separately the East and North West of England regions combined

Clinical condition	East of England region			East & North West of England regions combined		
	Number of prescriptions before the audit	Number of prescriptions during the audit	% Reduction (increase)* in number of prescriptions	Number of prescriptions before the audit	Number of prescriptions during the audit	% Reduction (increase)* in number of prescriptions
Acute periapical infection	1,194	706	40.9%	2,100	1,213	42.2%
Acute periodontal abscess	441	262	40.6%	678	356	47.5%
Pericoronitis	264	165	37.5%	451	289	35.9%
Infected socket	125	50	60.0%	194	107	44.8%
Acute ulcerative gingivitis	70	34	51.4%	168	102	39.3%
Sinusitis	25	11	56.0%	45	17	62.2%
Post surgical procedure	143	65	54.6%	283	151	46.6%
During root canal therapy	112	34	69.6%	114	35	69.3%
After root canal therapy	128	35	72.7%	140	50	64.3%
Periodontitis	96	38	60.4%	147	83	43.5%
Cellulitis	36	42	(16.7%)*	41	43	(4.9%)*
Pulpitis	51	10	80.4%	97	23	76.3%
Trismus	10	38	(280.0%)*	11	38	(245.4%)*
Gingivitis	18	1	94.4%	34	8	76.5%
Re-implantation of teeth	1	0	100.0%	1	1	0.0%
Salivary gland infection	0	3	(300.0%)*	0	5	(500.0%)*
Oral antral fistula	17	3	82.4%	18	4	77.8%
Others	166	64	61.4%	174	66	62.1%

therapeutic and prophylactic antibiotic prescribing. This took the format of an informal tutorial, working through all of the Faculty of General Dental Practitioners guidelines on adult antimicrobial prescribing,¹⁸ a copy of which was given to each participating dentist at the start of the session.

In order to fulfil the two aims of the audit, namely to reduce the number of antibiotics inappropriately prescribed by general dental practitioners, and

to increase the overall accuracy of each prescription, all eight groups of dentists then discussed and set their own standards to be reached.

Each dentist then audited their antibiotic prescribing for another six week period, with the information being collected and analysed in the same way as outlined above. At the end of that period, they met once again at their postgraduate medical centres, to be informed of the improvements, as well as to have

Table 6 The medical conditions and the number of prescriptions for which antibiotics were prescribed by the GDPs before and during the audit for prophylactic reasons, for both the East of England, and separately the East and North West of England regions combined.

Medical condition	East of England region		East & North West of England regions combined	
	Number of prescriptions before the audit	Number of prescriptions during the audit	Number of prescriptions before the audit	Number of prescriptions during the audit
Rheumatic fever	92	80	173	150
Murmurs	68	38	126	66
Valvular disease	77	56	123	102
Congenital heart defects	29	15	40	21
Coronary heart disease	13	7	29	18
Prosthetic joints	19	16	27	17
Radiotherapy / chemotherapy	0	1	9	3
Immunocompromised	13	13	39	31

an opportunity of further discussions and educational refinement from the local experts.

Data analysis

Frequencies were used to examine and describe the distribution of all the variables, with the changes in prescribing practices between the pre-audit and audit periods being tested manually for statistical significance using the chi-square test. In addition, some of the data were summated with those derived from the North West of England audit, in order to produce a larger sample of dentists to comment on.

RESULTS

The number of dentists who took part in this study was 212. In the pre-audit period 2,951 antibiotic prescriptions were issued, and during the audit this reduced by 43.6% to 1,665. When these data were combined with the North West of England's, a total of 387 dentists had prescribed 5,267 antibiotics in the pre-audit period, and 2,995 during the audit, resulting in a 43.1% reduction.

Antibiotics prescribed

Tables 1 and 2 show the six most frequent antibiotics prescribed during the pre-audit and audit periods of the study respectively, with a slight reduction in the number made for erythromycin and

a slight increase for those made for clindamycin, both as a result of the education previously received. Over both periods, amoxicillin and metronidazole were the two most commonly selected antibiotics, being prescribed on average 63.4% and 21.2% of occasions respectively. The antibiotics rarely prescribed included the cephalosporins, tetracyclines and anti-fungals.

Of the 2,951 antibiotic prescriptions issued in the pre-audit period, only 43% (1,268) were completely error free with respect to the prescribed dose, frequency and duration of use, but this rose significantly to 78.1% (1,300) during the audit, when 1,665 prescriptions had been made. ($\chi^2 = 531.6$, $df = 1$, $P < 0.001$).

Tables 3 and 4 show the number of occasions when it was deemed to have been either appropriate or not to have issued an antibiotic, together with the number of either erroneous or error free prescriptions, for the pre-audit and audit periods respectively.

In the pre-audit period, only 29.2% of prescriptions were considered justifiable using the published guidelines, but this rose significantly to 48.5% during the audit ($\chi^2 = 171.7$, $df = 1$, $P < 0.001$).

Clinical and medical conditions

Table 5 shows the clinical conditions recorded by the dentists for which antibiotics had been prescribed, together with

the number issued before and during the audit. The percentage change between the two periods is also shown, both for this study and for the East and North West of England regions combined. The reductions in the number of prescriptions issued following the educational session and the use of guidelines ranged from zero to 100% in the Eastern region, and between zero and 77.8% for the two regions combined. However, caution needs to be taken when assessing the significance of some of these figures due to the small numbers that are involved.

Table 6 shows the medical conditions for which prophylactic antibiotics were prescribed before and during the audit, for this study and the two regions combined. In both, the largest reduction in these prescriptions during the audit was in relation to murmurs, at 44.1% and 47.6% respectively.

Reasons for prescribing

Table 7 shows both the general reasons why, and the actual number of antibiotics that were prescribed in relation to the clinical and medical conditions previously listed. Overall, the majority of antibiotics were raised for therapeutic reasons, with only 10.5% and 13.6% for medical prophylaxis before and during the audit of this study respectively.

When the data on the individual reasons for prescribing were analysed in the present study as a proportion of the total number made during each relevant period, the following reductions in the audit period were found to be statistically significant (Table 8); pain ($\chi^2 = 13.5$, $df = 1$, $p < 0.001$), patient expectation ($\chi^2 = 11.2$, $df = 1$, $p < 0.001$), pressure of time/workload ($\chi^2 = 12.7$, $df = 1$, $p < 0.001$), uncertainty of the diagnosis ($\chi^2 = 9.3$, $df = 1$, $p < 0.01$), patient going on holiday/in case of problems ($\chi^2 = 12.0$, $df = 1$, $p < 0.001$), and other reasons ($\chi^2 = 8.9$, $df = 1$, $p < 0.01$).

In contrast, the proportion of the total number of prescriptions for the following reasons were found to have increased significantly during the audit period; localised fluctuant swelling ($\chi^2 = 8.1$, $df = 1$, $p < 0.01$), gross diffuse swelling ($\chi^2 = 54.5$, $df = 1$, $p < 0.001$), elevated temperature / evidence of systemic spread ($\chi^2 = 167.5$, $df = 1$, $p < 0.001$), and prophylaxis due to medical history ($\chi^2 = 7.7$, $df = 1$, $p < 0.01$).

In this study, and for the two regions

combined, the largest reductions in the actual number of prescriptions were seen for 'patient expectation', 'pressure of time and workload', as well as an 'uncertainty in the diagnosis' (Table 7).

Otherwise there were no significant changes seen in the reasons for prescribing between the pre-audit and audit periods for surgical prophylaxis, treatment delay, or for failed local anaesthesia.

DISCUSSION

The present study showed many similarities to the North West of England regional audit, with regard to the reduction in the overall number of antibiotics that were prescribed, the number of occasions when it was inappropriate to do so, together with a dramatic improvement in the accuracy of the antibiotic dosage, frequency and duration regimens.

For those antibiotics prescribed prophylactically for medical conditions, the main change noted between the pre-audit and audit periods related to those issued for cardiac murmurs, where after receiving the relevant education, the dental practitioners presumably were verifying both the status and the clinical need with the patients' physician first.

It was interesting to see that the reasons for prescribing which had significantly reduced during the audit in the North West of England were entirely matched in this study, with one notable exception, namely for localised fluctuant swellings, where there was in fact an unexplainable proportionate increase. Otherwise the other statistically significant proportionate increases in prescribing for various reasons seen during this audit, such as gross diffuse swelling, elevated temperature etc were entirely commensurate with the guidelines and education received by the practitioners.

However, while reductions were noted amongst those clinical conditions and general reasons for prescribing which current guidelines would suggest are inappropriate to cover for (eg acute periapical infection and pulpitis etc as in Table 5, or uncertainty of the diagnosis and pain etc as in Table 7), a reasonable number of these still recurred during the audit. This was despite the dentists having been given relevant literature to the contrary to read, supplemental to the educational component of the study.¹⁹⁻²⁹ As a consequence, it is suggested that should this study be replicated

Table 7 The reasons and the number of prescriptions for antibiotics prescribed by the GPs before and during the audit, showing the percentage change in the number of prescriptions between the two periods, for both the East of England, and separately the East and North West of England regions combined

Reason for prescribing	East of England region			East & North West of England regions combined		
	Number of prescriptions before the audit	Number of prescriptions during the audit	% Reduction (increase)* in number of prescriptions	Number of prescriptions before the audit	Number of prescriptions during the audit	% Reduction (increase)* in number of prescriptions
Localised fluctuant swelling	793	513	35.3%	1,517	867	42.9%
Gross diffuse swelling	309	302	2.3%	674	621	7.9%
Elevated temperature / evidence of systemic spread	74	197	(166.2%)*	253	374	(47.8%)*
Pain	1,372	681	50.4%	2,570	1,229	52.2%
Prophylaxis due to medical history	243	178	26.8%	498	360	27.7%
Prophylaxis following surgical procedure	158	70	55.7%	298	156	47.7%
Patient expectation	61	13	78.7%	182	49	73.1%
Pressure of time/ workload	56	10	82.1%	142	32	77.5%
Uncertainty of diagnosis	72	19	73.6%	152	35	77.0%
Treatment had to be delayed	179	110	38.6%	388	261	32.7%
Patient going on holiday / in case of problems	162	54	66.7%	201	61	69.7%
Failed local anaesthesia / un-cooperative patient	36	14	61.1%	62	28	54.8%
Other	127	43	66.1%	127	43	66.1%

elsewhere, a third cycle in the audit spiral could be considered, so that after the second meeting of the dentists, where the improved results would be discussed and education reinforced, there would then

be another opportunity for anonymous scrutiny and peer review to achieve even further improvement.

Indeed, one recent study has found that in relation to young children requiring

Table 8 The proportions (and percentages) on each occasion when an antibiotic either was or was not prescribed by the East of England GPs for the various clinical reasons, both before and during the audit, together with the Chi-square values and levels of statistical significance

Reason for prescribing	Period		X ²	p
	Pre-Audit	Audit		
Localised fluctuant swelling				
Yes	793 (26.9%)	513 (30.8%)	8.1	< 0.01
No	2,158 (73.1%)	1,152 (69.2%)		
Gross diffuse swelling				
Yes	309 (10.5%)	302 (18.1%)	54.5	< 0.001
No	2,642 (89.5%)	1,363 (81.9%)		
Elevated temperature / evidence of systemic spread				
Yes	74 (2.5%)	197 (11.8%)	167.5	< 0.001
No	2,877 (97.5%)	1,468 (88.2%)		
Pain				
Yes	1,372 (46.5%)	681 (40.9%)	13.5	< 0.001
No	1,579 (53.5%)	984 (59.1%)		
Prophylaxis due to medical history				
Yes	243 (8.2%)	178 (10.7%)	7.7	< 0.01
No	2,708 (91.8%)	1,487 (89.3%)		
Prophylaxis following surgical procedure				
Yes	158 (5.4%)	70 (4.2%)	3.0	n/s
No	2,793 (94.6%)	1,595 (95.8%)		
Patient expectation				
Yes	61 (2.1%)	13 (0.8%)	11.2	< 0.001
No	2,890 (97.9%)	1,652 (99.2%)		
Pressure of time / workload				
Yes	56 (1.9%)	10 (0.6%)	12.7	< 0.001
No	2,895 (98.1%)	1,655 (99.4%)		
Uncertainty of diagnosis				
Yes	72 (2.4%)	19 (1.1%)	9.3	< 0.01
No	2,879 (97.6%)	1,646 (98.9%)		
Treatment had to be delayed				
Yes	179 (6.1%)	110 (6.6%)	0.5	n/s
No	2,772 (93.9%)	1,555 (93.4%)		
Patient going on holiday / in case of problems				
Yes	162 (5.5%)	54 (3.2%)	12.0	< 0.001
No	2,789 (94.5%)	1,611 (96.8%)		
Failed local anaesthesia / un-cooperative patient				
Yes	36 (1.2%)	14 (0.8%)	1.4	n/s
No	2,915 (98.8%)	1,651 (99.2%)		
Other				
Yes	127 (4.3%)	43 (2.6%)	8.9	< 0.01
No	2,824 (95.7%)	1,622 (97.4%)		
Total	2,951 (100%)	1,665 (100%)		

dental treatment under a general anaesthetic, both the uncertainty of the likely delay between referral and treatment on the part of the practitioner, and the presence of pain were motivating factors to prescribe an antibiotic. The same study showed that children who have not had antibiotics improve clinically, in terms of swelling and temperature in the long term. There is a need therefore to disseminate this information to practitioners, and advise on the use of analgesics to manage pain while the patient awaits the provision of definitive treatment.³⁰

Early in this study it was noted that by following the North West of England audit protocols no assessments would be made as to whether the choice of antibiotic for each particular condition had been based on the published guidelines. Despite this identified limitation, the decision of the majority of participating dental tutors was not to amend the original protocol, so that direct comparisons and data amalgamation could be made with the North West of England study.

The decision not to assess ‘correct antibiotic choice’ against the guidelines ultimately proved fortuitous, as it gave the local microbiological consultants the opportunity, where relevant, to update the four year old guidelines with some subtle changes in the antibiotic choice and regimens to follow when prescribing for certain situations; such as substituting clindamycin for erythromycin as the third choice antimicrobial to use for acute dentoalveolar infections.³¹ Had this been stifled to maintain conformity with the guideline recommendations, some patients could have been disadvantaged from not receiving treatment based upon best contemporary pharmacological evidence, as illustrated by a recent report on azithromycin.³²

Appropriate, contemporaneous, and accurate prescribing of antibiotics is therefore essential not only to treat conditions effectively, but also to reduce antibiotic resistance. For example, in a recent study, the prevalence of penicillin resistant bacteria isolated from samples of pus obtained from incisions of acute dentoalveolar soft tissue swellings was significantly higher from a group of patients who had been prescribed a penicillin based antibiotic for a mean of two days before drainage was established, as compared to another group who had not received penicillin.³³

Not surprisingly, drug resistant organisms such as MRSA engender great fear among patients prior to hospital admission,³⁴ given the morbidity and mortality associated with this organism, the latter of which has risen 15-fold in England and Wales over the last decade.³⁵

Measures to reduce the prevalence of MRSA in hospitals, such as microbiological pre-admission screening, and segregation on the ward,³⁶ lessen the opportunity for cross contamination between patients. Such endeavours should be complemented by reducing antibiotic resistance in general through improved prescribing practices by all health care workers across the United Kingdom.

CONCLUSION

The present study supports the conclusion of the previous North West of England's report,¹⁶ that clinical audit in conjunction with guidelines and an educational component with feedback is effective in reducing inappropriate and inaccurate antibiotic use amongst general dental practitioners.

Improvements in prescribing can be achieved by dental practitioners making good use of their tri-annual 15 hours of clinical audit,³⁷ through participating in a collaborative audit such as this one, which was modelled on the favourably received North West of England project.¹⁷ Benefits to the patient of better prescribing practices include more effective treatment of conditions, and a reduction in antibiotic resistant micro-organisms.

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