Chapter 10

Interventions to Optimise Antibiotic Prescribing in Hospitals: The UK Approach

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1. INTRODUCTION

A large body of evidence supports a correlation between antibiotic usage and resistance, but confirmation of a causal relationship has proved illusory, the evidence for such a relationship having been exclusively circumstantial. Recently, however, Lopez-Lozano *et al*. (2000), using time-series analysis, a form of mathematical modelling, have demonstrated convincingly that antibiotic prescribing is the driving force behind the emergence of resistance to these drugs. This is an important development because it holds out hope that reducing antibiotic prescribing will lead to a corresponding reduction in the incidences of resistance—a theory that remains unconfirmed as investigators who have evaluated the efficacies of interventions to reduce antibiotic prescribing have, for the most part, used cost, prescribing levels or, less frequently, appropriateness of prescribing, rather than resistance rates, as outcome measures. In the few cases where resistance rates have been employed as an outcome measure, efforts to determine the impact of the interventions have been undermined by the effects of confounding variables, most notably infection control measures. Finally, even if it were possible to totally eliminate inappropriate antibiotic prescribing, resistance rates will continue to be driven upwards by appropriate prescribing.

Notwithstanding uncertainties regarding the effects of interventions to optimise antibiotic prescribing on rates of resistance, several government and

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other authoritative bodies (Government Response to the House of Lords Select Committee on Science and Technology Report, 1998; House of Lords Select Committee on Science and Technology, 1998; NHS Executive, 1999; Report from the Invitational EU Conference on the Microbial Threat, 1998; Sub-group on Antimicrobial Resistance of the Standing Medical Advisory Group, 1998) have called for reductions in inappropriate antibiotic usage. This challenge, albeit well motivated, reveals a lack of understanding of the complex relationships between antibiotic usage and antibiotic resistance and the obstacles associated with successfully controlling the prescribing of these drugs. More importantly, while all of these agencies have specified the outcome, none has identified the process by which it is to be achieved. The failure to provide hospitals with guidance on interventions to reduce inappropriate antibiotic prescribing explains, at least in part, why, 4 years after the challenge was issued, many hospitals have not yet implemented a formal antibiotic control programme. One could be forgiven for expecting that the paper produced by the Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance, entitled *Guidelines for the Prevention of Antimicrobial Resistance in Hospitals* (Shlaes *et al*., 1997), might contain clear evidence-based guidelines/recommendations for optimising antibiotic prescribing, but this is not the case. Indeed, to date, no such guidelines have been published. In 1999, the British Society for Antimicrobial Chemotherapy and the Hospital Infection Society convened a joint working party on optimising antibiotic prescribing in hospitals in order to address this issue.

2. JOINT BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY/ HOSPITAL INFECTION SOCIETY WORKING PARTY ON OPTIMISING ANTIBIOTIC PRESCRIBING IN HOSPITALS

2.1. Membership of the Working Party

The membership of the Working Party comprises five medical microbiologists (one of whom is a trainee), three infectious diseases physicians, one surgeon, and one pharmacist; there are also five members from outside the United Kingdom (three from Europe and two from the United States) who are recognised for their expertise in the field of optimising antibiotic usage and who serve as corresponding advisors.

2.2. Literature search

The Working Party began its deliberations by carrying out a systematic review of the published literature on interventions aimed at optimising antibiotic prescribing in hospitals. Relevant publications were identified by three independent electronic searches. In the first, MEDLINE, EMBASE, and the Cochrane database of clinical trials were searched from 1980 onwards using a broad range of search terms. The second search was conducted in MEDLINE (1966–2000), using PubMed and OVID, and the Cochrane database, and employed terms which differed from those used in the first search. Finally, the third search was of the Cochrane Effective Practice and Organisation of Care (EPOC) specialised register which, itself, was compiled by searching MEDLINE (from 1966), Health STAR (from 1975), and EMBASE (from 1980). There were no language limitations. In addition, the references section of each paper was reviewed and any articles not identified by electronic search were obtained and the process repeated; failing to supplement the electronic searches with a manual search would have resulted in a failure to identify at least one third of the articles.

2.3. Systematic review

The electronic and manual searches yielded 670 articles, of which 306 published from 1980 onwards contained original data about interventions in hospitals. These 306 studies were then evaluated for eligibility for inclusion in a Cochrane EPOC review. The principal criteria for inclusion related to: study design (only randomised controlled trials, RCTs, controlled clinical trials, CCTs, controlled before and after studies, CBAs, and interrupted time series, ITS, with ≥ 3 data points before and after the intervention being eligible); minimum methodological criteria (a study must involve objective measurement of provider performance/behaviour or patient outcome(s), and relevant and interpretable data must be presented or obtainable from the investigators); and EPOC scope (a study must involve the evaluation of the effect(s) of behavioural/educational, financial, organisational, or regulatory intervention(s)). Of the 306 studies, 80 (26.1%), comprising 38 ITS, 24 RCTs or CCTs, 11 CBAs, and 7 others, fulfilled the inclusion criteria. Two hundred and twenty-six (74%) studies were excluded for the following reasons: uncontrolled before and after studies (141, 62.4%); inadequate ITS (75, 33.2%); and inadequate CBAs or CTs (10, 5%). There was a significant upward trend with time in terms of the percentage of studies with robust designs, but, even in the final 4-year period (2000–3), only 36.2% of studies were eligible for inclusion in the review.

ITS, which accounted for approximately 48% of the included studies, was the most common type of design. In most cases, the results of these studies were analysed by comparing the means of the pre- and postintervention data points. However, this format can lead to inappropriate, indeed erroneous, conclusions. For example, an upward trend in the data points before the intervention has been implemented may cause the effect of the intervention to be underestimated. Conversely, a downward trend before the intervention has been implemented may lead to the effect of the intervention being overestimated. The EPOC group has recommended that segmented regression analysis be used to estimate the magnitude of the effects of interventions. However, of the 38 ITS studies, the investigators in 23 (60.5%) determined the means of the pre- and postintervention data points, but failed to subject the data to statistical analysis thereby precluding a conclusion regarding whether or not the effect of the intervention was statistically significant, and those in 11 (29%) determined the means of the data points and subjected the results to statistical analysis, but reached the wrong conclusion, leaving only four (10.5%) groups of investigators who employed segmented regression analysis (two of the studies having been carried out by the same group). The advantage of adopting segmented regression analysis to assess the data is that it provides information about the speed of the impact of the intervention and whether or nor the effect is sustained. For example, in a study carried out by Belliveau *et al*. (1996), in which vancomycin prescribing was restricted in an attempt to reduce the incidence of vancomycin-resistant enterococci, the volume of vancomycin dosing was used as the outcome measure. As soon as the intervention was implemented, there was a significant reduction in the number of doses prescribed. However, almost immediately thereafter, dosing levels gradually increased until, by the eleventh month, they had returned to preintervention levels. This trend would not have been detected if the results had been analysed by comparing the means of the pre- and postintervention data points. It is clear, therefore, that the method of analysing the data has a profound influence on the way in which the results are interpreted.

It would be reasonable to expect that the 80 studies which fulfilled the criteria for inclusion in the review were robust in terms of their design and execution. This is, however, not the case: a high proportion of these studies suffering from one or more serious methodological flaws. Although the review has not yet been completed, several conclusions can be drawn from the findings to date.

1. Both the quality and quantity of the evidence in the published literature which supports the efficacies of the interventions are disappointing.
2. The majority of published studies used inadequate control methods, thereby precluding efforts to determine whether any change in practice/outcome was attributable to the intervention.

3. ITS accounted for almost 50% of the studies included in the review; in most of these, inappropriate statistical analysis of the results of the studies overestimated the magnitudes of the effects of the interventions.
4. Many of the studies which fulfilled the criteria for inclusion in the review suffer from methodological flaws.
5. Suboptimal methods of analysing the data generated by some studies led the investigators to reach incorrect conclusions.
6. For some interventions, not even a single study fulfilled the inclusion criteria, there being, therefore, no published evidence to support them.
7. In several studies, up to four interventions were implemented simultaneously, thereby precluding efforts to discern the relative contribution of each measure to the outcome.
8. Only a very small minority of studies employed resistance rates as an outcome measure.
9. Only a very small minority of studies compared the efficacies of interventions.
10. In some cases, assessment of the impact of an intervention was undermined by the effects of confounding variables, most frequently, infection control measures.
11. Owing to the absence of robust evidence from published studies, most, if not all, of the recommendations made by the Working Party will probably represent a consensus of expert opinion.

3. INTERVENTIONS

As the Working Party had not completed the systematic review of the literature at the time of writing, it is not possible to make evidence-based recommendations regarding interventions to optimise antibiotic prescribing in hospitals. However, it is likely that some or all of the measures described below will be recommended for implementation.

3.1. Educational/persuasive vs restrictive/coercive interventions

Interventions fall into two categories, educational or persuasive, and restrictive or coercive. Educational interventions, for example, pharmacy bulletins and newsletters, lectures, conferences, and handbooks are preferable, but it is perceived that, alone, they are of limited value in terms of facilitating judicious antibiotic usage. Moreover, without constant reinforcement to maintain their impact, their effects will be only temporary.

Although there is little evidence to support the efficacies of restrictive interventions specifically to control antibiotic usage, such measures, in general, have consistently been shown to be more effective than educational strategies (not surprisingly as prescribers can only rarely be relied upon to demonstrate goodwill) and their impacts are more enduring. Bamberger and Dahl (1992) compared the impact of voluntary restriction of selected antibiotics (ceftazidime and ceftriaxone) with that of a strict control policy. When restriction was voluntary, only 24.2% of the usage of these drugs was in compliance with local guidelines, compared with 85.4% when restriction was enforced; coincidently, expenditure on these agents was reduced significantly and susceptibility rates among isolates of *Enterobacter cloacae* and *Pseudomonas aeruginosa* increased. In another study (Himmelberg *et al*., 1991), removal of a restrictive policy led to a 158% increase in usage of previously restricted drugs and a 103% increase in expenditure on these agents. Nonetheless, restrictive interventions are effective only if they are enforced, and enforcement may lead to adversarial relations between prescribers, who have been shown to perceive them as dictatorial and to prefer less coercive measures, and those healthcare workers (usually pharmacists) who have accepted responsibility for enforcing them. Moreover, controlling antibiotic prescribing may be more difficult in smaller hospitals where support mechanisms are not usually available; such hospitals tend to rely less on restrictive interventions than on education to influence prescribing practices.

3.2. Core interventions

The following interventions represent the minimum measures that should be implemented in all hospitals.

3.2.1. Antibiotic Control Plan

The Antibiotic Control Plan (ACP) should be the cornerstone of a hospital's efforts to influence the volume and appropriateness of antibiotic usage. The measures which comprise the plan should be devised, implemented, promoted, enforced, and their efficacies monitored by the Antibiotic Control Committee, a subcommittee of the Drugs and Therapeutics Committee. The Committee should have executive powers and should be chaired by a senior consultant with specialised knowledge of infectious diseases and antibiotics (either a microbiologist or an infectious diseases physician), although this is not essential. The membership should also comprise a microbiologist (if not

the chairman), a physician, a surgeon, a trainee doctor, and a pharmacist. The responsibilities of the committee can be summarised as follows:

1. To devise an antibiotic formulary.
2. To produce guidelines for antibiotic prescribing.
3. To develop and implement educational programmes.
4. To develop and implement other interventions for controlling and promoting prudent antibiotic prescribing.
5. To monitor, through the audit process, the efficacies of and compliance with the interventions implemented locally.
6. To undertake surveillance of antibiotic usage within each speciality, providing feedback of prescribers' own antibiotic practices in relation to those of peers or a standard.
7. To undertake regular (2-yearly) reviews of the interventions which have been implemented.

3.2.2. Antibiotic formulary

An antibiotic formulary is simply a list of drugs available for use within a hospital. Formulary control has been shown to be the most direct and effective means of influencing antibiotic prescribing and reducing antibiotic expenditure and resistance rates, without adversely affecting patient care; it can also have a positive educational impact on prescribers. The following standards apply to formulary development and implementation:

1. The antibiotics included in the formulary should be limited to the minimum necessary to provide effective prophylaxis and therapy, thereby enabling pharmacies to negotiate favourable prices. Ideally, only one antibiotic in each class should be included, thereby eliminating duplicate agents and reducing the number of drugs stocked by the pharmacy. Each drug should be chosen on the basis of efficacy, propensity to promote the development of resistance, pharmacokinetic properties, pharmacodynamic properties, side-effect and safety profiles, tolerability, and cost.
2. The choice of agents should be influenced by local susceptibility patterns.
3. The drugs included in the formulary should be placed into categories, with restrictions on the use of certain agents, based on special indications, breadth of spectrum, toxicity, cost, potential to be misused, and propensity to promote the development of resistance.
4. The formulary should be reviewed periodically, specifically regarding the need to include antibiotics which have recently become available or to delete redundant agents and to determine whether drugs which have been

subject to abuse or to which there have been marked increases in rates of resistance should be reassigned to a category to which restrictions apply.
5. Compliance with the formulary should be audited.

3.2.3. Enforcing formulary restrictions

The drugs which are included in the formulary can be classified as unrestricted (i.e., can be prescribed by any prescriber without the need for prior approval) or restricted (i.e., available only if usage conforms with guidelines that have been developed by the Antibiotic Control Committee or following discussion with a designated "expert"). The success of a formulary will depend on how rigorously compliance with it is enforced as prescribers frequently fail to adhere to formulary restrictions. There are two methods of enforcing compliance with formulary restrictions.

The first of these is the antibiotic order form which requires written justification to prescribe, or to continue prescribing, drugs included on the restricted list. The information sought on the order form has varied from centre to centre, but has included the following: whether the prescription is for prophylaxis or treatment (empirical or definitive); site of infection; clinical criteria on which the diagnosis of infection is based; the suspected or confirmed cause(s) of the infection; patient-related information, such as age, weight, underlying disease, renal and hepatic function, and known allergies; and drug-related information, such as dosage, frequency, route of administration, and duration. The forms are evaluated by a pharmacist and approval of the use of the antibiotic granted or withheld according to guidelines devised by the Antibiotic Control Committee. This intervention has been shown to be effective in terms of controlling antibiotic usage, limiting the duration of prophylaxis and treatment and facilitating audit. However, it is labour-intensive and sophisticated information technology is required in order for it to be implemented. Moreover, prescribers often fail to complete the forms or the quality of the information is poor or inadequate or both. The lack of sufficient resources in most UK hospitals would make this strategy impracticable.

The alternative method is the requirement to seek approval for the use of antibiotics on the restricted list from an "expert" who is usually either a medical microbiologist or an infectious diseases physician. Normally, approval will be granted if the proposed usage falls within predetermined guidelines. In the United States, approval is sought, during or out of normal working hours, from an infectious diseases physician. In theory, it would be feasible to implement such a strategy in hospitals in the United Kingdom that have large numbers of infectious diseases physicians and/or microbiologists on staff. However, in most hospitals, this will not be the case and a compromise would be necessary. During routine working hours, a pharmacist would refer the prescription to

a medical microbiologist or infectious diseases physician who, following discussion with the prescriber, would either approve it or recommend an alternative regimen. If the drug has been prescribed out of hours, it would be issued for a finite period (e.g., 24–48 hr), at the end of which pharmacy staff would notify a local expert who would either approve the prescription or not. This strategy is more suited to use in the United Kingdom, although its implementation would be facilitated by computerised prescribing.

A third, noncoercive method of controlling the use of restricted drugs has been proposed by Williams *et al*. (1985). It involves prospective monitoring of patients prescribed the targeted drugs by an expert. If the prescription is considered appropriate, the prescriber is not contacted, but if the prescription is considered inappropriate, an informal approach is made to the prescriber who is advised either to discontinue the antibiotic or to switch to an alternative, equally effective, less expensive regimen. This strategy was well received by the prescribers in the hospital in which it was evaluated, involved them in negligible additional effort, was educational for those who had prescribed inappropriately, and led to substantial cost savings. It was, however, time- and labour-expensive for the individuals monitoring the prescriptions.

3.2.4. Automatic antibiotic stop-order policy

The aim of an automatic antibiotic stop-order policy is to limit the durations of unnecessarily prolonged prescriptions for therapy and prophylaxis. In the United States, implementation of such a policy is a requirement of the Joint Commission on Accreditation of Hospitals, while in the United Kingdom, a survey carried out by a Working Party of the British Society for Antimicrobial Chemotherapy (1994) revealed that only 26% of the 539 respondents employed such an intervention.

In its simplest form, the policy requires prescribers to specify a duration for each antibiotic prescription, regardless of whether it is for prophylaxis or treatment. In theory, this could be done on a voluntary basis. However, as prescribers can rarely be relied upon to comply voluntarily, it must be enforced in order to be effective. This responsibility is usually devolved to pharmacists who are empowered to discontinue those prescriptions for which durations have not been specified after an agreed period, usually from 48 to 72 hr. Those drugs which have been discontinued must be re-ordered if patients are to continue receiving them, although the policy can be overridden if the prescriber stipulates a duration. An educational programme should always precede the introduction of a stop-order policy and, ideally, prescribers should be notified 24 hr before the stop-order is implemented, thereby preventing lapses in continuous treatment. Stop-order policies have been shown to be effective means of ensuring that antibiotics are not inadvertently administered for excessive

periods and have enabled the durations of treatment of patients with some types of infections to be standardised. Problems include the potential risks to patients associated with premature discontinuation of therapy (although this may be more theoretical than real), the need for human resources (pharmacists) to enforce the policy, reluctance by pharmacists to act as 'policemen' and antagonism from prescribers whose prescriptions have been discontinued. In addition, 48–72 hr is widely perceived to be an excessive duration for surgical prophylaxis. Many of these difficulties can be overcome by computerised prescribing which obviates the need for pharmacists to enforce the policy.

A variation of the stop-order policy is the pre-printed antibiotic prescription/order form on which prescribers must specify the indication for the antibiotic(s) they want a patient to receive, that is, as prophylaxis or empirical or definitive therapy. If an antibiotic has been designated as prophylaxis, administration is discontinued after 24 hr; alternatively, the pharmacy dispenses only enough doses to cover a 24-hr period. If the prescriber indicates that the antibiotic is to be given as empirical therapy, the prescription is discontinued after 48–72 hr. This stimulates the prescriber to reassess the need for antibiotic therapy and the appropriateness of the antibiotic regimen in the light of additional clinical information, as well as the results of laboratory and radiological investigations which should be available by that time, rather than simply continuing with a regimen that is ineffective or inappropriate. Finally, if a prescription is designated as definitive therapy, it will be administered, commonly for between 5 and 7 days. The policy is enforced by pharmacy staff or implemented through a computer-assisted antibiotic order entry programme. All of the above can be overridden if the prescriber specifies a duration. Again, the introduction of an antibiotic order form should be preceded by an educational programme and prescribers should be given 24 hr notice if a prescription is to be discontinued. The disadvantages of this type of intervention include the need for adequate human resources and the potential for antagonism between prescribers and pharmacists.

3.2.5. Guidelines for antibiotic prescribing

In general, the implementation of clinical guidelines can lead to improvements in clinical practice by reducing variations in the methods and standards of care, improving the appropriateness and quality of care, reducing the cost of care, improving the cost-effectiveness of care, serving as educational tools, and promoting evidence-based decision making. Specifically in relation to antibiotic usage, clinical guidelines have been shown to promote more prudent use of these drugs and to reduce expenditure on them; they may also lead to reductions in the incidences of antibiotic-resistant pathogens.

Guidelines for antibiotic prescribing are becoming increasingly popular as a means of influencing clinicians' practice. In a survey of consultant microbiologists and hospital pharmacists in the United Kingdom (Working Party of the British Society for Antimicrobial Chemotherapy, 1994), 62% of respondents indicated that antibiotic guidelines were available in their hospitals. More recently, a 1998 survey of hospitals in the United States participating in Project ICARE (Intensive Care Antimicrobial Resistance Epidemiology) revealed that 70% of these institutions had introduced clinical guidelines for antibiotic usage (Lawton *et al*., 2000). The success of the guidelines will depend on many factors but, most importantly, the rigour and commitment used in developing, disseminating, implementing, and evaluating them.

3.2.5.1. Guideline development

There have been concerns about the quality of many of the clinical guidelines produced by specialty societies on the grounds that they do not conform to the basic principles of guideline development (Grilli *et al*., 2000); the implementation of inappropriate recommendations may compromise patient care. A detailed description of the methodology by which guidelines are developed is outside the remit of this chapter. Readers, and particularly those contemplating the development of guidelines, should refer to the websites of guideline development groups, such as the Appraisal of Guidelines Research and Evaluation in Europe (AGREE) collaboration (http://www.agreecollaboration.org) or the Scottish Intercollegiate Guideline Network (SIGN) (http:// www.sign.ac.uk), as well as reviews by Brown (2002), Finch and Low (2002), Kish (2001), Natsch and van der Meer (2003), Peetermans and Ramaekers (2002), and Thomson *et al*. (1995). However, the essential features of guideline development can be summarised as follows:

1. There should be guidelines for prophylaxis and both empirical and definitive therapy.
2. The group developing the guidelines should be multidisciplinary and there should be a sufficient number of members (6–10) with expertise and experience in the subject of the guidelines in order to allow it to be adequately explored and to ensure that the guidelines are credible. The group should comprise at least one individual with the skills necessary to conduct literature and systematic reviews. There should be input from all stakeholders, including trainees, who are the prescribers who are most likely to use them, in order to ensure that there is 'ownership' of the guidelines, thereby increasing the likelihood that they will be implemented.
3. The development group should determine whether or not evidence-based guidelines on the same topic already exist. If so, they can be adopted as they are or adapted to suit local circumstances.

4. The guidelines must be based on a systematic review of the scientific evidence. In order to minimise the risk of bias, the literature should be identified according to an explicit search strategy, selected according to defined inclusion criteria, and assessed against consistent methodological standards. The method by which the literature is obtained, along with the search terms and the period of the search, should be specified.
5. As scientifically robust evidence is not always available it is likely that many guidelines will be hybrids of varying degrees of evidence and expert opinion. To ensure transparency of the recommendations that comprise the guidelines, the recommendations should be graded according to the strength of the evidence supporting them. The grading system should be validated, with the grading based on an objective measurement of the study design and quality and of the consistency, clinical relevance, and external validity of the evidence.
6. The guidelines should not be excessively long, that is, no more than 20–25 pages.
7. They should be simple, clear, non-controversial, clinically relevant, flexible, applicable to day-to-day practice, and available in a user-friendly format.
8. The antibiotics recommended in the guidelines should take account of the pathogens encountered locally and their susceptibility patterns.
9. As well as providing recommendations for optimal selection, the guidelines should include information regarding dosage, route of administration, duration, alternatives for patients who are allergic to first-line agents, and adjustments of dosages for patients with impaired renal function.
10. For prophylactic use, the guidelines should specify the procedures for which antibiotics are needed (or not needed) and the optimal agents, their dosages, and the timing, route, and duration of administration.
11. The guideline development group should identify evidence that is lacking and areas for further research.
12. The development group should identify sample outcome measures that would form the basis for auditing both the process and outcome of the guidelines.
13. The guidelines should be reviewed by respected peers who are not members of the guideline panel, but who are experts in the relevant field.
14. Guidelines are not static. They should be reviewed at periodic intervals that should be specified (e.g., 2-yearly) and updated to take account of advances in medical knowledge, changes in clinical practice and local circumstances, and the outcome of guideline evaluations. Any modifications of the guidelines must be the result of the same rigour and commitment as the original recommendations.

Guidelines can be developed nationally or locally. Those developed locally by the clinicians who will use them are less likely to be scientifically valid than

those developed nationally by Royal Colleges and working parties of specialty societies because local groups lack the clinical, managerial, and technical skills, as well as the time and financial resources, needed for the task. Moreover, expertise at the local level is unlikely to be sufficiently broad, and personal opinions may introduce bias into the decision-making process. Locally produced guidelines must be no less robust than those produced nationally if patients are to receive optimal care. On the other hand, prescribers may disagree with or distrust guidelines written by remote national 'experts.' Guidelines are more likely to be implemented if users have participated in their development. Consequently, fewer resources are needed for effective dissemination and to promote implementation, compared with national guidelines for which greater emphasis must be placed on these phases of the process. A reasonable compromise would be to adapt national evidence-based guidelines (where such guidelines exist) for local use, a strategy that may be adequate to ensure prescribers' compliance.

3.2.5.2. Guideline dissemination

One reason why guidelines are ineffective is that the target prescribers are often unaware of their existence. Dissemination then is the process of bringing guidelines to the attention of their intended users with the aim of increasing awareness and influencing knowledge, attitudes, and behaviour.

Dissemination can be achieved in a variety of ways: publication in journals, newsletters, local reports or documents, junior doctors' handbooks, configuration into a brief and portable format that is readily accessible to clinicians, posters on wards and in relevant departments, patient literature, group educational programmes, and personal visits. The optimal strategy has not been determined. Publication in medical journals, especially general medical journals, has, to date, been the most commonly used method, but is regarded as a poor means of disseminating guidelines and has a low likelihood of implementation. Direct mailing to relevant practitioners is seen as a more effective measure, but it is still of limited efficacy, although the impact of this intervention can be enhanced by making the guidelines visually attractive and/or by staging their delivery in manageable 'chunks' of information. In general, however, passively delivered interventions, such as written communications, have minimal abilities to achieve even temporary changes in behaviour. Grimshaw and Russell (1994) have claimed that the more overtly educational the dissemination strategy, the greater the likelihood that the guidelines will be adopted and the more lasting their impact, provided that dissemination is linked to an effective implementation strategy.

3.2.5.3. Guideline implementation

Simply developing and disseminating guidelines, irrespective of how well they are done, is of limited value in terms of affecting improvements in

healthcare unless the guidelines are implemented. Implementation is the process of ensuring that guidelines are introduced into clinical practice. Regrettably, the resources dedicated to developing guidelines have not been matched by those to promote compliance with them and, consequently, there is strong evidence that guidelines are often not adopted. Surveys have shown that compliance can vary from 20% to >90%, depending on the nature of the guideline, the specific clinical problem it is designed to address, the patient group being targeted, the mode of implementation and the definition of adherence. The most experienced practitioners may be the least likely to comply with guidelines. Cabana *et al*. (1999) identified three domains of barriers to implementation which related to: knowledge (lack of awareness or familiarity with the guidelines); attitudes (lack of agreement with the guidelines, lack of trust in the guidelines, i.e., low outcome expectancy, lack of self-confidence, i.e., self-efficacy, or the inertia of previous practice); and behaviour (external barriers which may be guideline-, patient- or environment-related). Others have suggested the following additional explanations for practitioners' failure to adhere to guidelines:

1. Guidelines may not be written for practising clinicians, but merely represent a summary of the current state of knowledge, that is, they lack scientific validity.
2. Important stakeholders may not have been represented on the group that developed the guidelines.
3. Clinicians may choose to ignore guidelines for nonclinical reasons, such as financial incentives or fear of litigation.
4. Guidelines may lack applicability to individual patients.
5. Local opinion leaders may not have endorsed the guidelines.
6. There may be inefficiencies of the healthcare system.

Guidelines should facilitate changes in practice, but if the changes are to be sustained, measures designed to promote implementation of guidelines must also change clinicians' knowledge, attitudes, and beliefs. Active educational interventions, such as seminars that are devoted exclusively to the guidelines and where potential users are given the opportunity to discuss them, are more likely to be effective than didactic lectures or simply including the guidelines as part of an educational programme. However, education alone is insufficient to ensure compliance. Other interventions that have been shown in at least some studies to promote adoption of guidelines and to lead to improvements in practice behaviour and clinical outcome include the following:

1. Endorsement by local and national professional organisations.
2. Incorporation into routine practice by local opinion leaders.

3. Dissemination of guidelines by department heads.
4. Audit of compliance with guidelines, with feedback of results to clinicians.
5. Peer review.
6. Printed patient-specific reminders at the time of consultations to prompt clinicians to use guidelines, for example, by attaching the guidelines to clinical notes or by including them on desktop computers.
7. General reminders of guidelines.
8. Making guidelines available to prescribers when they are making clinical decisions. This process has been facilitated by computer-assisted decision support programmes such as that described by Pestotnik *et al*. (1996), although the efficacy of this intervention has not been validated independently and the effects on patient outcomes have not been adequately assessed.
9. Promoting 'ownership' of guidelines by involving potential users in their development; alternatively, local adaptation of national guidelines may be sufficient to convey a sense of ownership.
10. Incorporation of guidelines into service contracts between purchasers and providers.
11. Educational outreach visits ('academic detailing'), that is, pre-arranged face-to-face discussions between a detailer (a trained educator such as a pharmacist) and a practitioner at the latter's place of work with the aim of persuading the practitioner to change behaviour through information and evidence (Soumerai and Avorn, 1990). To date, this has been the most effective and most lasting method of promoting compliance and has the advantage of allowing those clinicians who most need to change their practices to be targeted. On the other hand, it is expensive and labour-intensive and concerns have been raised about whether or not it is effective outside the research setting.

Any one or a combination of interventions improves compliance with guidelines to varying degrees. However, because most studies of the efficacies of these interventions have involved multiple strategies, it has not been possible to discern the relative contribution of each one. For this reason, and because many of the studies suffered from methodological flaws and because there have been very few comparative studies, efforts to identify the most effective intervention(s) have been frustrated. In general, multiple measures have proved more effective than single interventions and a combination of strategies is, therefore, most likely to have the maximum impact on guideline implementation.

3.2.5.4. Evaluation

Evaluation is the assessment of the efficacy of the guidelines, with the aim of ensuring that they have produced the intended changes in both practice and

outcome. Audit is the most effective means of achieving this objective, but it is essential to evaluate all of the components of the guideline process, not simply outcome, as they are inextricably linked. In other words, improvements in clinical outcome will not be realised unless guidelines are received, read, and adopted.

3.2.6. Laboratory control and the role of the medical microbiologist/infectious diseases physician

The clinical microbiology laboratory and specialists in infectious diseases (clinical microbiologists and infectious diseases physicians) can make important contributions to a hospital's programme to optimise antibiotic prescribing. Laboratory control can be achieved in a variety of ways:

1. By promoting optimal usage of diagnostic services, ensuring that specimens are appropriate, clinically relevant, and timely. The submission of inappropriate specimens, in particular, those taken from sites that are not clinically infected and those obtained after antibiotic therapy has been initiated, should be discouraged as they may lead to inappropriate treatment.
2. By undertaking selective susceptibility testing, that is, including only those antibiotics which are listed in the hospital formulary.
3. By appending clinical interpretations to laboratory reports (e.g., casting doubts on the significance of laboratory isolates) when such comments are appropriate.
4. By not determining, or by withholding, the susceptibilities of clinical isolates when there is inadequate clinical information to enable an informed opinion about significance or when there are doubts about the significance of these isolates. Failure to do so will, in at least some cases, cause inexperienced prescribers to assume that the results have been interpreted by the laboratory as being clinically significant and to initiate antibiotic therapy inappropriately.
5. By selective reporting of antibiotic susceptibility test results, that is, reporting the susceptibility patterns of only a limited number of agents which are appropriate treatment of the patient from whom the specimen has been obtained; ideally, these drugs should be the least expensive and most narrow-spectrum available.
6. By undertaking rapid identification and susceptibility testing of clinical isolates. It has been demonstrated that rapid provision of the results of susceptibility testing is more likely than conventional testing to lead to timely changes to appropriate treatment and to have a demonstrable impact on the care and outcome of hospitalised patients with infections. However, this will mean that laboratories will be required to adopt aggressive reporting

strategies in order to bring the results to the attention of prescribers for appropriate action. Furthermore, rapid methods have reduced abilities to detect some types of inducible resistance, thereby leading to false reports of susceptibility.

7. By collecting local surveillance data and reporting trends and susceptibility patterns in order to guide optimal empirical therapy.

As well as playing a pivotal role in the development and implementation of the various interventions which comprise a hospital's ACP, clinical microbiologists and infectious diseases physicians provide timely advice to colleagues regarding diagnosis, the most appropriate specimens which should be submitted for microbiological investigations and optimal empirical and definitive therapy. Compared with nonspecialists in the management of patients with infectious diseases, they have been shown to distinguish more accurately between infected and noninfected patients, to prescribe appropriate empirical and definitive therapy more often and at an earlier stage and to be associated with higher survival and cure rates. They also prescribe fewer antibiotics overall and fewer broad-spectrum antibiotics specifically and are more likely to convert from intravenous (iv) to oral treatment and from broad- to narrow-spectrum agents when culture and susceptibility test results are available. Patients treated by such specialists experience shorter mean lengths of hospital stay, fewer relapses and readmissions, higher satisfaction scores, and shorter times to return to regular activities compared with patients under the care of nonspecialists. Yet, in a survey conducted by a Working Party of the British Society for Antimicrobial Chemotherapy (1994), only 75% of respondents, who were consultant medical microbiologists, indicated that they provided a clinical consultative service. Not every patient about whom an opinion is sought needs to be seen directly and much useful advice can be given over the telephone. However, it is only at the bedside that a patient's clinical status can be accurately assessed and it is at the bedside where the greatest influence over antibiotic prescribing can be exerted. Face-to-face contact between microbiologists/infectious diseases physicians and prescribers promotes confidence in the former, increases the likelihood of future consultations, and is educational.

3.2.7. Educational interventions

As stated previously, educational interventions have had only minimal effects on antibiotic prescribing and the impacts of those which have been shown to be effective were short-lived unless they were constantly reinforced. On the other hand, education complements the effects of other interventions, including those which are more restrictive or coercive, and must be regarded as the foundation of a hospital's efforts to optimise antibiotic prescribing; it is

potentially the only means by which prescribers can be persuaded to accept ownership of the problem of antibiotic resistance. In order to have a sustained effect on prescribing behaviour it is necessary to change prescribers' underlying attitudes and beliefs. The interventions which have been shown in several studies to be the most effective in terms of changing practice are: audit and feedback, computer-assisted decision support, educational outreach visits, local opinion leaders, mass media interventions, and printed educational material. However, prescribers tend to revert to preintervention practices once the study has been terminated. Those who have had experience of trying to change prescribers' practices will empathise with the views of Sbarbaro (2001): "Changing physician behaviour is considered by many to be an exercise in futility—an unobtainable goal intended only to produce premature ageing in those seeking the change. The more optimistic might describe the process as uniquely challenging."

A long-term strategy which might be more effective than changing the behaviour of existing prescribers is to 'mould' the behaviour of future prescribers, that is, medical students. As well as understanding the need for prudent prescribing, medical students must be taught how to use the services of the diagnostic laboratory effectively, inappropriate investigations leading to inappropriate prescribing.

3.2.8. The role of the hospital pharmacist

Although clinical pharmacists in the United States have for many years occupied high-profile roles and have been extremely effective in terms of controlling anti-biotic usage, this resource has not, to date, been adequately utilised in the United Kingdom, despite the obvious benefits of doing so. Indeed, the costs of employing one or more pharmacists to fulfill the role of antibiotic utilisation coordinator/infectious diseases pharmacist can be offset by savings on antibiotic expenditure. As well as being a member of the Antibiotic Control Committee and enforcing the interventions implemented by the Committee (such as formulary restrictions and automatic antibiotic stop-order policies), the pharmacist has an educational role (promoting good and cost-effective prescribing practices), monitors compliance with clinical guidelines and other interventions, monitors antibiotic consumption (to highlight inappropriate antibiotic usage), and undertakes audit initiatives (including evaluating the effects of clinical guidelines on outcome and antibiotic resistance patterns). Pharmacists should be provided with modern computer facilities in order to enable them to expedite these functions and should promote the introduction of electronic prescribing. For a more detailed discussion of the role of the pharmacist in antimicrobial management, the reader is referred to Chapter 13, this volume, by Knox *et al*.

3.3. Other interventions

Several other strategies for optimising antibiotic prescribing in hospitals have been proposed and/or evaluated. Although there is a paucity of robust evidence in the literature to support the efficacies of most of these interventions, and some are controversial, at least a few may have benefits and may eventually find places in the antibiotic control programmes of some hospitals.

3.3.1. 'Streamlining'

'Streamlining' is the conversion of initial therapy, based on the results of culture and susceptibility testing and clinical response, from a broad- to a narrow-spectrum regimen, from combination therapy to monotherapy or from newer, expensive drugs to older, less-expensive drugs with equivalent efficacies. Too often, patients are left to complete initial courses of therapy because they are responding to them and because prescribers are reluctant to change the regimens. Although there is little evidence of the efficacy of streamlining, the collective experience in many centres suggests that it is feasible, effective, and safe. Its implementation has been associated with substantial cost savings, lower incidences of toxicity, and reduced selective pressures for resistance and it has been shown to have a marked educational impact on prescribers.

3.3.2. Intravenous (iv)-oral switch therapy

The conversion from a parenteral to an oral antibiotic regimen, also known as sequential antibiotic therapy, is a form of streamlining. The oral alternative may simply be a different formulation of the same drug, a drug belonging to the same class of antibiotics or a drug belonging to a different class of antibiotics. Regardless, the most important criteria are that the oral agent has therapeutic efficacy that is comparable to that of the iv drug, that it is active against the cause of the infection and that it has good oral bioavailability. The conversion should be implemented in accordance with recognised criteria.

Treatment by the oral route has several advantages. Oral formulations are easier to administer and less expensive (in terms of both acquisition and administration costs) and are associated with lower incidences of complications (phlebitis and catheter-related bloodstream infections). Perhaps most importantly, they facilitate early discharge from hospital, thereby reducing the cost of care and the likelihood of patients being exposed to or transmitting antibiotic-resistant potential pathogens. The implementation of such a programme is not without its difficulties, its success depending upon the collaborative efforts of the parental clinical team, the hospital pharmacy, members of the microbiology department, and nursing staff.

3.3.3. Combination therapy

The practice of using combination therapy is an extension of effective antituberculous and antihuman immunodeficiency virus therapy, that is, the administration of two or more antibiotics reduces the likelihood of the emergence of resistant strains. However, while some investigators outside of the setting of tuberculosis have demonstrated a trend towards less frequent emergence of resistance in patients given combinations of drugs, and others have reported higher clinical and bacteriological cure rates (the latter, in principle, helping to reduce transmission of antibiotic-resistant strains), most of those who have compared the efficacy of combination therapy with that of monotherapy (usually a β-lactam/aminoglycoside combination and a β-lactam alone respectively) have failed to show that the former is superior to the latter in terms of preventing the emergence of resistant strains. The combination approach also leads to considerable hidden costs and may be associated with drug interactions (antagonism) at the receptor sites, an increased frequency of superinfection (secondary to greater disruption of the normal flora) and a greater likelihood of adverse drug reactions. With the exception of antituberculous therapy, there is currently insufficient evidence to justify the routine use of combination treatment as a general means of minimising the emergence of antimicrobial resistance.

3.3.4. Therapeutic substitution

Therapeutic substitution involves replacing a prescribed antibiotic with one having a different chemical structure, but belonging to the same therapeutic class and having comparable pharmacokinetic and pharmacodynamic properties and clinical efficacy. This intervention has been applied broadly to those therapeutic classes having little diversities among constituent drugs or large disparities in drug prices. Examples of antibiotics to which the strategy might apply are cephalosporins, aminoglycosides, and quinolones. A therapeutic substitution is initiated by a hospital's drug and therapeutic committee and is implemented within the context of the formulary system. The principal motivation is cost savings. The practice has been widely adopted throughout both the United States and the United Kingdom.

The challenges of therapeutic substitution include identifying appropriate therapeutic alternatives, obtaining prescriber approval before making a therapeutic substitution, adequately monitoring the effects of therapeutic substitution on patient outcome, dealing with toxic reactions and drug interactions, and identifying true savings after taking account of the costs of implementing and administering the intervention, adverse events, and drug administration.

3.3.5. 'Cycling' (rotation)

'Cycling' is the scheduled withdrawal of a class of antibiotics (or a specific member of a class) and substitution with a different class (or a specific member of that class). This may be followed after a specified interval by a third or a fourth substitution, but, in order to fulfil the definition, the initial regimen must be re-introduced at a later stage and the cycle repeated. The duration of each cycle is based on either local susceptibility patterns or a predetermined time period. Cycling has normally involved substitution of one class of antibiotics with another, as opposed to substitution with a member of the same class (which shares resistance mechanisms), although, in some studies, one aminoglycoside was replaced with another. Cycling is not the same as simply withdrawing one drug and replacing it with another. The rationale behind the intervention is that the more frequently an antibiotic is prescribed, the more likely resistance to it will develop. Withdrawal of an antibiotic for a proscribed period of time will limit the selective pressures exerted by that agent, thereby allowing rates of resistance to it to stabilise or decrease during the period of restriction and ensuring that its efficacy is intact when it is re-introduced at a later date in place of a substitute. Each cycle is timed to occur before the emergence of significant levels of resistance to the substitute drug. The objective, therefore, is to maintain the total mass of any drug below the critical level that leads to the emergence of resistance to it.

Notwithstanding the current popularity of cycling, data supporting its efficacy are limited. Most of the investigators who claimed to have evaluated cycling assessed withdrawal/substitution; the initial regimen was not re-introduced. Of the studies that actually investigated cycling, most did not fulfil the criteria for inclusion in a systematic review, the majority being uncontrolled before-and-after studies. Of the three which fulfilled these criteria, interpretation of the effects of cycling on resistance rates was undermined, owing to a lack of standardisation, the impact of confounding variables, in particular, infection control interventions, the failure to differentiate clinical isolates which were simply colonising patients from those causing infection and the administration of "off-cycle" drugs to as many as 50% of patients. Furthermore, each of the studies published to date involved only a single intensive care unit, thereby precluding efforts to make generalisations. Finally, the results of a study which used mathematical models suggest that cycling will always be inferior to "mixed" antibiotic use (the simultaneous prescribing of alternative drugs belonging to different classes) at the population level (Bonhoeffer *et al*., 1997).

In conclusion, the efficacy of cycling, in terms of preventing or reversing the trend towards increasing antibiotic resistance, has not been demonstrated. Indeed, the investigators in four studies described the rapid re-emergence of

strains resistant to the initial antibiotic when it was re-instated. There remains a need for large, well-designed, CCTs employing high-quality epidemiological tools, sophisticated resistance mechanism and molecular typing analyses, and effective and consistent infection control interventions. A great many issues relating to cycling need to be resolved before undertaking such trials, let alone implementing this intervention on a routine basis.

3.3.6. Computer-assisted decision support

Computer-assisted decision support provides prescribers with information relevant to individual patients at the bedside when the decision to administer antibiotics is made, this being the most critical period in terms of influencing the choice of treatment. Recommendations on prophylaxis and empirical and definitive therapy are based on patient data, local susceptibility patterns, local practice guidelines and costs of formulary drugs, all of which must be programmed into the hospital information system. As well as advising on the choice of antibiotics, the system recommends dosages and durations and alerts prescribers to incorrect dosages, routes of administration and intervals between doses, resistant pathogens, cost-effective alternatives, drug incompatibilities, the need to monitor serum drug concentrations, etc. In its most highly developed form, this computer-driven aid has been shown to lead to reduced antibiotic usage and expenditure, increased appropriateness of antibiotic prescribing, improved clinical outcome, and reduced incidences of adverse drug reactions, without leading to increased incidences of resistance (Evans *et al*., 1998; Pestotnik *et al*., 1996). However, its efficacy has not been confirmed by well-designed clinical trials and the benefits in terms of patient outcome have not yet been adequately assessed. Moreover, there is a requirement for highly sophisticated information technology systems which are not widely available in hospitals in the United Kingdom, although they are currently under development in some centres.

3.4. Outcome measures

Measuring the impact of the interventions implemented in a hospital in order to optimise antibiotic prescribing is fraught with problems. For example, simply determining the incidences of antibiotic-resistant organisms before and after the introduction of an intervention does not allow the relative contribution of the intervention to be distinguished from that of infection control measures. However, the following parameters might be used as a basis for assessing the efficacies of the strategies which have been introduced.

1. Auditing compliance with the intervention.
2. Monitoring changes in total drug usage, expressed in terms of Defined Daily Doses (DDDs), before and after implementation and annually.

3. Monitoring changes in the usage of targeted drugs (in DDDs) before and after implementation and annually.
4. Monitoring changes in the mean durations of antibiotic prescriptions.
5. Monitoring changes in the mean durations of hospital stay.
6. Monitoring changes in the appropriateness of prescriptions.
7. Monitoring changes in the antibiotic susceptibilities of target organisms before and after implementation.

4. CONCLUSIONS

1. Most, if not all, of the recommendations which will be made by the Working Party, once the systematic review of the literature has been completed, are likely to be based on a consensus of expert opinion, rather than robust published evidence.
2. A multifaceted approach, that is, one involving a combination of interventions, will be needed to achieve a maximum impact on prescribing behaviour.
3. It may not be feasible or practicable to implement all of the interventions described above (indeed, it may not even be possible to implement all of the core interventions) in each hospital and it will, therefore, be necessary to develop a programme of interventions that suits local circumstances and needs.
4. The interventions that are implemented will need to be enforced and their efficacies monitored through the audit process.
5. Hospital management will need to demonstrate support for the programme developed by the Antibiotic Control Committee by making available to it adequate resources to enable the interventions introduced to control antibiotic usage to be implemented and enforced.

REFERENCES

Bamberger, D. M. and Dahl, S. L., 1992, Impact of voluntary vs enforced compliance of third-generation cephalosporin use in a teaching hospital. *Arch. Intern. Med*., **152**, 554–557.

Belliveau, P. P., Rothman, A. L., and Maday, C. E., 1996, Limiting vancomycin use to combat vancomycin-resistant *Enterococcus faecium*. *Am. J. Health Syst. Pharm.*, **53**, 1570–1575.

Bonhoeffer, S., Lipsitch, M., and Levin, B. R., 1997, Evaluating treatment protocols to prevent antibiotic resistance. *Proc. Natl. Acad. Sci. USA*, **94**, 12106–12111.

Brown, E.M., 2002, Guidelines for antibiotic usage in hospitals. *J. Antimicrob. Chemother*., **49**, 587–592.

Cabana, M. D., Rand, C. S., Powe, N. R., Wu, A. W., Wilson, M. H., Abboud, P.-A. C. *et al*., 1999, Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA*, **282**, 1458–1465.

Evans, R. S., Pestotnik, S., Classen, D. C., Clemmer, T. P., Weaver, L. K., and Orme, J. F., Jr., 1998, A computer-assisted management program for antibiotics and other antiinfective agents. *N. Engl. J. Med*., **338**, 232–238.

Finch, R. G. and Low, D. E., 2002, A critical assessment of published guidelines and other decision-support systems for the antibiotic treatment of community-acquired respiratory tract infections. *Clin. Microbiol. Infect*., **8**(Suppl. 2), 69–92.

Government Response to the House of Lords Select Committee on Science and Technology Report, 1988, *Resistance to Antibiotics and Other Antimicrobial Agents*, CM 4172. The Stationery Office, London.

Grilli, R., Magrini, N., Penna, A., Mura, G., and Liberati, A., 2000, Practice guidelines developed by specialty societies: The need for a critical appraisal. *Lancet*, **355**, 103–106.

Grimshaw, J. M. and Russell, I. T., 1994, Achieving health gain through clinical guidelines. II: Ensuring guidelines change medical practice. *Qual. Health Care*, **3**, 45–52.

Himmelberg, C. J., Pleasants, R. A., Weber, D. J., Kessler, J. M., Samsa, G. P., Spivey, J. M. *et al*., 1991, Use of antimicrobial drugs in adults before and after removal of a restriction policy. *Am. J. Hosp. Pharm*., **48**, 1220–1227.

House of Lords Select Committee on Science and Technology, 1998, *Resistance to Antibiotics and Other Antimicrobial Agents*. The Stationery Office, London.

Kish, M. A., 2001, Guide to development of practice guidelines. *Clin. Infect. Dis*., **32**, 851–854.

Lawton, R. M., Fridkin, S. K., Gaynes, R. P., McGowan, J. E., and the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) Hospitals, 2000, Practices to improve antimicrobial use at 47 US hospitals: The status of the 1997 SHEA/IDSA position paper recommendations. *Infect. Cont. Hosp. Epidemiol*., **21**, 256–259.

Lopez-Lozano, J.-M., Monnet, D. L., Yague, A., Burgos, A., Gonzalo, N., Campillos, P. *et al*., 2000, Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: A time series analysis. *Int. J. Antimicrob. Agents*, **14**, 21–31.

Natsch, S. and van der Meer, J. W. M., 2003, The role of clinical guidelines, policies and stewardship. *J. Hosp. Infect*., **53**, 172–176.

NHS Executive, 1999, *Resistance to Antibiotics and Other Antimicrobial Agents*. HSC 1999/049, NHS Executive, Leeds, UK.

Peetermans, W. E. and Ramaekers, D., 2002, Clinical practice guidelines in infectious diseases. *Neth. J. Med*., **60**, 343–348.

Pestotnik, S. L., Classen, D. C., Evans, R. S., and Burke, J. P., 1996, Implementing antibiotic practice guidelines through computer-assisted decision support: Clinical and financial outcomes. *Ann. Intern. Med*., **124**, 884–890.

Report from the Invitational EU Conference on The Microbial Threat, 1998, *The Copenhagen Recommendations*. Ministry of Health, Ministry of Food, Agriculture and Fisheries, Copenhagen, Denmark.

Sbarbaro, J. A., 2001, Can we influence prescribing patterns? *Clin. Infect. Dis*., **33**(Suppl. 3), S240–S244.

Shlaes, D. M., Gerding, D. N., John, J. F., Jr., Craig, W. A., Bornstein, D. L., Duncan, R. A. *et al*., 1997, Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: Guidelines for the prevention of antimicrobial resistance in hospitals. *Clin. Infect. Dis*., **25**, 584–599.

Soumerai, S. B. and Avorn, J., 1990, Principles of educational outreach (‘academic detailing’) to improve clinical decision making. *JAMA*, **263**, 549–556.

Sub-Group on Antimicrobial Resistance of the Standing Medical Advisory Group, 1998, *The Path of Least Resistance*. Department of Health, London.

Thomson, R., Lavender, M., and Madhok, R., 1995, How to ensure that guidelines are effective. *BMJ*, **311**, 237–242.

Williams, R. R., Gross, P. A., and Levine, J. F., 1985, Cost containment of second-generation cephalosporins by prospective monitoring at a community teaching hospital. *Arch. Intern. Med*., **145**, 1978–1981.

Working Party of the British Society for Antimicrobial Chemotherapy, 1994, Hospital antibiotic control measures in the UK. *J. Antimicrob. Chemother*., **34**, 21–42.