THE PATH OF LEAST RESISTANCE

MAIN REPORT

Standing Medical Advisory Committee
Sub-Group on Antimicrobial Resistance

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1 INTRODUCTION

In July 1997, concerned about the growing problem of antimicrobial resistance, the Chief Medical Officer, Sir Kenneth Calman, asked the Standing Medical Advisory Committee (SMAC) to examine the issue of antimicrobial resistance in relation to clinical prescribing practice. SMAC responded by setting up an inter-disciplinary Sub-Group with the following Terms of Reference:

BOX 1

TERMS OF REFERENCE

In the light of the increasing clinical importance of resistance to antimicrobial drugs, to:
- identify the major and emerging problems of antimicrobial resistance in clinical practice
- identify clinical practices that may predispose to the development of resistance
- identify practices that might help to limit the development and spread of resistance to antimicrobial agents
- identify priorities for changing practice in the use of antimicrobial agents
- advise on how such changes might most effectively be achieved for both professionals and the public

Membership of the Sub-Group (set out in Section 25) included cross-representation from the Standing Advisory Committees for Dentistry, Pharmacy, Nursing and Midwifery, the veterinary profession, consumers and the pharmaceutical industry.

This Report represents the outcome of the Sub-Group's deliberations.

In introducing the Report, it may be helpful to draw attention to specific features of antimicrobial therapy that distinguish it from all other forms of medicinal treatment.

FIRST

The majority of the population will, at some time or other in their lives, take antimicrobial agents. Apart from simple analgesics, no other drugs are in such widespread use.

SECOND

The efficacy of an antimicrobial agent in any individual patient is affected by its previous use in other individuals, which may have selected for the development of resistance to the drug. This situation does not apply for any other kind of medicine: taking a drug to lower blood pressure in the wrong dose, or unnecessarily, may be deleterious for that individual, but it will not affect the efficacy of the medication for others. Unlike other diseases, infections (communicable diseases) are the results of interactions between two dynamic populations, human beings and micro-organisms.

THIRD

There is probably no other area in which patients' expectations, and doctors' perceptions of those expectations, play such an important role in determining whether or not to prescribe. This means that any strategy to reduce unnecessary prescribing cannot be targeted only at professionals. Rather, it must also address the needs of the consumer for clear information about the risks and benefits of antimicrobial agents, and about the circumstances in which it is appropriate for the doctor *not* to prescribe.

FOURTH	Resistance to antimicrobial agents is a natural evolutionary response of microbes to antimicrobial exposure. While certain clinical prescribing practices exacerbate the development of resistance, it is much less clear that changing those practices will reduce levels of resistance. A realistic expectation would be that more appropriate prescribing would prevent the situation deteriorating further. It is vital that unrealistic expectations are not generated by the recommendations in this Report, or by other initiatives to improve antimicrobial prescribing.
FIFTH	The part played by veterinary prescribing in the development of antimicrobial resistance in human pathogens is important for some, but not all, pathogens. This is the subject of a major review by the Government's Advisory Committee on the Microbiological Safety of Food. Debate over the relative contributions of clinical and veterinary prescribing to the development of antimicrobial resistance in man must not be allowed to delay the implementation of initiatives to improve clinical prescribing practices.
SIXTH	The use of antimicrobial agents as animal growth promoters is distinct from veterinary prescribing and is not performed under veterinary supervision. Its role in the selection of resistance is a major concern, especially as it risks undermining new antibiotics, now being developed, even before these enter human use.
SEVENTH	It is important to recognise that our best efforts, in this country, to minimise resistance may be frustrated by a lack of comparable initiatives abroad. Early and demonstrable successes in modifying clinical prescribing practice in the UK may provide a helpful model for others.
FINALLY	Good antimicrobial prescribing will have other beneficial effects – in particular, a reduction in the incidence of adverse effects. Adverse effects are always unwelcome, but an adverse event arising from an unnecessary prescription is doubly so.

The recommendations in this Report are directed towards ensuring that best practice in antimicrobial prescribing becomes routine practice. This will require a willingness, on the part of health care professionals and the public alike, to treat antimicrobial agents as a valuable and non-renewable resource, to be treasured and protected in their own, and everyone else's, interest.

RECOMMENDATIONS

There is a huge literature, growing daily, on antimicrobial resistance in relation to clinical prescribing. Not all of it is soundly evidence-based and many fundamental questions have not been addressed. Hence, the Sub-Group has made no attempt to produce an exhaustive set of recommendations for minimising resistance in every clinical situation.

Rather, since the aim of this Report is to make a genuine difference, we have taken the pragmatic approach of concentrating on recommendations where the 'pay-back' in terms of the potential benefit seems, on the current evidence, likely to be greatest. Thus, we have concentrated on recommendations related to prescribing for commonly encountered conditions and on proposals for developing support systems to help prescribers make evidence-based decisions, which involve patients and carers in the decision-making process.

In the light of research on how to promote change in professional and societal behaviour, the Report recommends a co-ordinated approach with a variety of proposals ranging from educational programmes, through organisational changes, to financial inducements for industry. The recommendations are presented in a framework which is addressed to policy and decision makers at national, regional and local levels – including industry – and to prescribers and the public. Within the framework, there are recommendations aimed at helping general medical practitioners (who undertake 80% of all antimicrobial prescribing) to optimise their own prescribing practices, hence minimising the selection of resistance.

PRESCRIBING IN THE COMMUNITY

Most infections present to general practitioners (GPs); consequently, 80% of antimicrobial prescribing for patients in the UK is in the community. This Report, therefore, concentrates on community prescribing of antimicrobial agents. **We recommend** that there should be a national Campaign on Antibiotic Treatment **(CAT)** in primary care on the theme of: 'Four things you can do to make a difference' (see Box 2). In making recommendations aimed at influencing doctors' prescribing habits, we acknowledge the importance and influence of patients' expectations and demands on the decision-making process. We see these as two sides of the same coin: modifying patients' expectations, through a process of public education, will make it easier for GPs to adhere to the recommendations. Hence, **we recommend** that the **CAT** must be matched by a National Advice to the Public **(NAP)** campaign aimed specifically at supporting the initiative in primary care. A key feature of the **NAP** campaign should be to highlight the benefits of 'cherishing and conserving your normal bacterial flora'.

BOX 2

FOUR THINGS YOU CAN DO

- no prescribing of antibiotics for simple coughs and colds
- no prescribing of antibiotics for viral sore throats
- limit prescribing for uncomplicated cystitis to 3 days in otherwise fit women
- limit prescribing of antibiotics agents over the telephone to exceptional cases

We recommend that further support for appropriate prescribing in primary care be provided by developing and promulgating evidence-based national guidelines for the management of certain infections, under the aegis of the National Institute for

Clinical Excellence. Guidelines would aim to minimise unnecessary use of antimicrobial agents and to ensure that when needed, the most appropriate antimicrobial agent and regimen are used so as to ensure the best possible clinical outcome and reduce the risk of resistance developing. **We recommend** that such national guidelines are adapted for local use during the development of Health Improvement Plans. Health Authorities will need to co-ordinate guideline development and use with Primary Care Groups/Local Health Groups based upon local microbiological and epidemiological advice.

The best of guidelines are of no value if they are not used. To make the incorporation of the guidelines into everyday practice as effort-free as possible, **we recommend** that they should be integrated within computerised decision-support systems as soon as possible (Section 16.1.2). A number of these are under development, and some are currently being piloted in general practice. These guidelines should also be promulgated widely through the medical literature.

PRESCRIBING IN HOSPITALS

Hospital prescribing accounts for only about 20% of all human prescribing of antimicrobial agents in the UK. Nevertheless, resistance problems are greatest in hospitals, reflecting the fact that (i) the prescribing is concentrated in a small locale, intensifying selection for resistance, (ii) many hospitalised patients have severe underlying diseases that render them susceptible to infection by otherwise harmless 'opportunist pathogens' that have been adept at acquiring resistance and (iii) the high concentration of susceptible patients facilitates the spread of infection. Thus, prescribing in hospitals poses some different issues from those in primary care. However, hospital clinicians would benefit as much as GPs from the availability of computer-aided decision-support systems, into which suitably adapted national prescribing guidelines can be integrated. Information technology for clinical use tends not to be as well-developed in hospitals as in primary care, but is being established. Therefore, **we recommend** that studies be undertaken in selected hospitals to develop and test one or more prototype decision-support systems. To be fully effective, these computer-based advisory systems should include information from local antimicrobial sensitivity profiles. These in turn should feed into regional and national surveillance databases.

PRESCRIBING GUIDELINES

We recommend that local prescribing information should, wherever possible, be harmonised with that in the British National Formulary (BNF) and other formularies. Guidelines and formularies should also take account of the proposed national evidence-based guidelines to be produced under the aegis of the National Institute for Clinical Excellence. All local prescribing guidelines should take their cue from these national guidelines to avoid confusion and re-invention of the wheel. **We recommend** that all such local guidelines should include, as a minimum, certain standard items of information on the drug, dosage and duration of therapy (Section 16.1.1).

EDUCATION

The development of guidelines and their widescale introduction will have important and beneficial implications for the education of health care professionals involved in prescribing antimicrobial agents. **We recommend** that greater emphasis than hitherto should be placed on teaching about such prescribing in medical and dental schools, as well as in the undergraduate curricula for pharmacists and nurses. **We recommend** also that teaching about antimicrobial agents should be better integrated with teaching about the infections for which they are used. This enhanced emphasis on education in the use of antimicrobial agents should be carried over into continuing medical, dental, nursing and professional education and development. Similar concepts apply in veterinary medicine.

The whole population, not just those destined to become health care professionals, would benefit from more education about the benefits and disadvantages of antimicrobial agents. In addition to health education material aimed at adults, **we recommend** that teaching about antibiotics should be included as part of the health education in the National Curriculum. Such teaching should highlight the benefit of a normal bacterial flora.

SURVEILLANCE OF RESISTANCE

Effective surveillance is critical to understanding and controlling the spread of resistance. Not only does surveillance monitor the existing situation, it allows the effects of interventions to be tested. **We recommend** that a strategic system for resistance surveillance of antimicrobial resistance should be developed as swiftly as possible, and that this should cover the whole of the UK. Discussions to develop such a system are taking place between the Public Health Laboratory Service (PHLS), British Society for Antimicrobial Chemotherapy and various colleagues in Scotland and Ireland (Section 17). It is vital that the system being developed is adequately resourced to provide high-quality information and **we so recommend**.

RESEARCH

National and local surveillance will give invaluable guidance to the many health service and university projects needed to investigate the drivers of resistance and the effects of interventions (Section 17). Basic research is also needed on the mechanisms of antimicrobial resistance and their spread. **We recommend** that research into antimicrobial resistance should become a high priority for all funding bodies concerned with health care and biomedical research. We note, with grave concern, the downgrading of medical microbiology as an academic speciality in many teaching hospitals, including several with distinguished records of work on antimicrobial resistance.

HYGIENE, INFECTION CONTROL AND CROSS-INFECTION

Not all problems merit the ubiquitous 'more research needed' recommendation. In some cases the solutions are well known; it is implementation that is deficient. This is true for certain aspects of infection control. In hospitals, the guidance – in the form of the Cooke report [1] – is there to be followed. At its heart is attention to cleanliness and hygiene in all their manifestations. These extend from the thoroughness of the work done by cleaning staff to simple hand-washing by health care professionals in contact with patients. The issue of infection control, although intimately bound up with problems of antimicrobial resistance – particularly in hospitals and other health care environments – was outside the Terms of Reference of our Sub-Group. Nevertheless, we believe that it is so fundamental to preventing the spread of resistant organisms, not only in hospitals but also in the community, that **we recommend** consideration be given to producing guidance on infection control in the community, especially in nursing and residential homes. This may need to await clarification of the roles and responsibilities of Health and Local Authorities in the control of infection in community settings.

VETERINARY AND AGRICULTURAL USE

Antimicrobial agents are used under veterinary supervision for the treatment and prophylaxis of infection. Some agents are also used *without this supervision* as growth promoters. These aspects were, strictly, outside our remit although our Sub-Group had cross-representation from the Advisory Committee on the Microbiological Safety of Food, whose Working Group on Microbial Antibiotic Resistance in Relation to Food Safety is expected to report later this year. Nevertheless, we recognise that the use of antibiotics in animals has a profound influence on the development of antimicrobial resistance in human pathogens and **our general recommendation** would be that the use of antibiotics in animals should be guided by the same

principles as those for prescribing in humans – namely, they should be used only for those clinical conditions where their use is likely to provide a genuine health benefit (Section 12.12). **We recommend** that alternative means of animal husbandry be developed so that the use of antibiotics as growth promoters can be discontinued.

IMPLICATIONS FOR INDUSTRY

If our recommendations are followed, they should have the effect, *inter alia*, of reducing antibiotic usage. There may be financial implications for the pharmaceutical industry, upon whose profitability the development of new antibiotics depends. Therefore, **we recommend** that consideration be given by the appropriate bodies to finding ways – through pricing and other mechanisms – of ensuring that investment in the development of new antibiotics remains commercially viable for the industry.

In addition, **we recommend** that industry should be encouraged to undertake studies of optimum prescribing regimens for new antimicrobial agents, for each indication and in adults and children as appropriate. This evidence-based information should be included in the Summary of Product Characteristics (SPC) for each product, as set out in the Product Licence and the Product Data Sheet. **We recommend** that the licensing authorities should have due regard to an antimicrobial agent's potential to select resistance as well as to its efficacy and safety.

INTERNATIONAL CO-OPERATION

In the field of antibiotic prescribing, this country cannot consider itself an island. International prescribing practices have a major influence on the development and spread of resistant organisms and their genes. In particular, resistant organisms in Europe enjoy as much freedom of movement – only in larger numbers – as their human hosts. Hence, **we recommend** that every effort is made by the Government to raise the profile of antimicrobial resistance as a major public health issue meriting priority action from all Member States of the European Union.

EXPECTATIONS

We wish to emphasise that our Report should not generate unrealistic expectations. Even stopping altogether the prescribing of certain antimicrobial agents may not lead to an appreciable reduction in the levels of resistance to those drugs, even over several years. However, we hope to achieve a slowing of the rate at which resistance develops. This may buy a few more years of therapeutic usefulness for certain antimicrobial agents, until such times, hopefully, as they may be replaced by new and novel compounds. Different considerations may then apply to compounds as they enter into therapeutic use, so as to build in, from the outset, safeguards to minimise the development of resistance.

NATIONAL STRATEGY

Our aim has been to produce recommendations that can constitute the first phase of a national strategy for minimising the development of antimicrobial resistance. We recommend, as part of this phase, the establishment of a small National Steering Group (NSG) charged with ensuring that these recommendations are implemented and that their effects, on prescribing practice and on the development of resistance, are monitored. The NSG, which might need to establish a small number of expert groups to take forward specific aspects of the recommendations, should report to the Chief Medical Officer within a year on progress with – and lessons learned from – implementing Phase 1 of the strategy. Thereafter, the CMO may wish to consider asking SMAC to reconvene this Sub-Group, in order to provide a suitable inter-disciplinary forum for the development of the next phase of the strategy, building on the results of various pilot and other studies to evaluate the effectiveness of the recommendations in this Report.
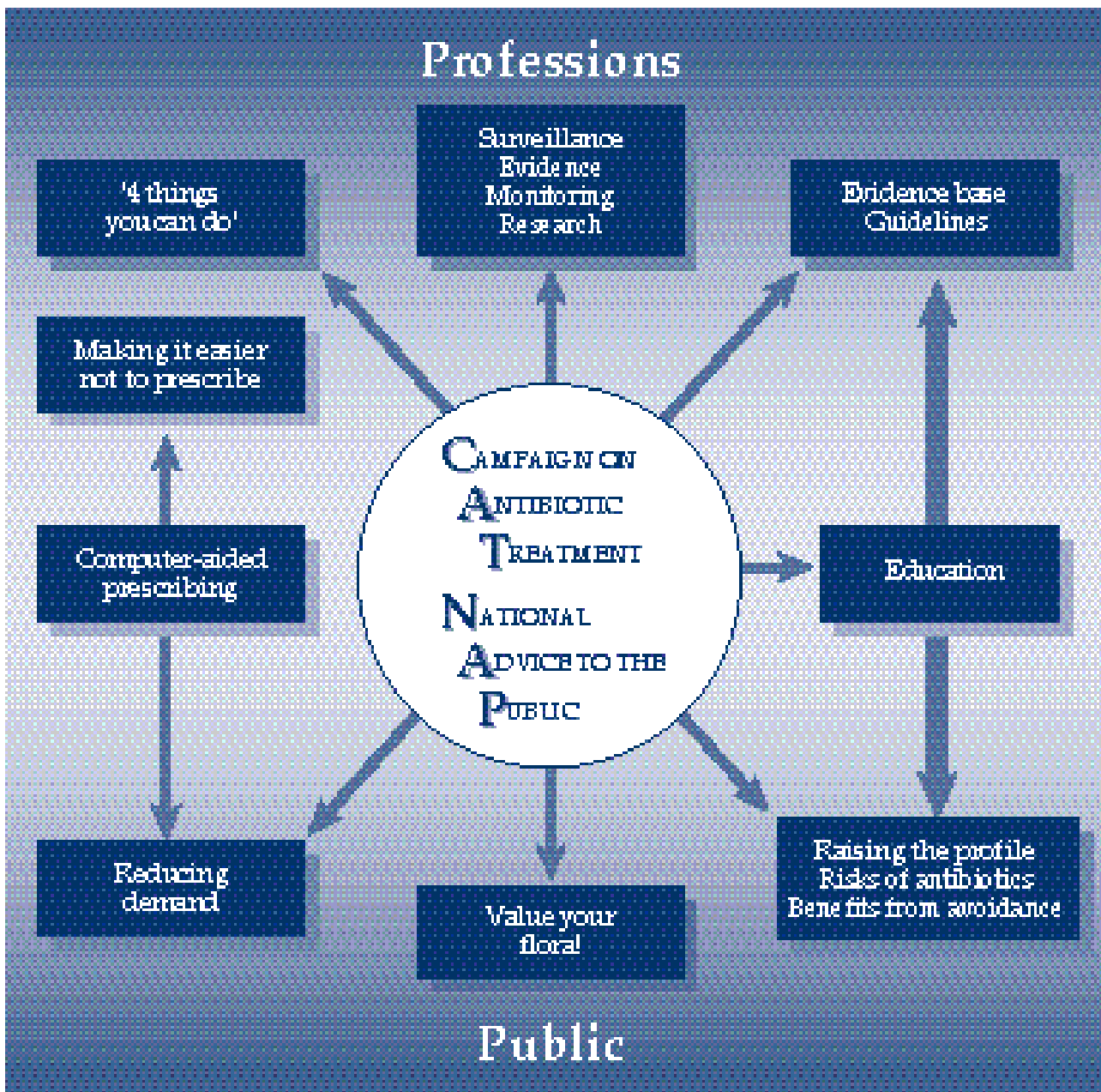
Professions

'4 things you can do'

Surveillance
Evidence
Monitoring
Research

Evidence base
Guidelines

Making it easier not to prescribe

Computer-aided prescribing

CAMPAIGN ON
ANTIBIOTIC
TREATMENT
NATIONAL
ADVICE TO THE
PUBLIC

Education

Reducing demand

Value your flora!

Raising the profile
Risks of antibiotics
Benefits from avoidance

Public

LOOKING INTO THE ABYSS

For two human generations antimicrobial agents have altered expectations of life and death. The fever hospitals on the edge of town have gone, as have the tuberculosis sanatoria. In the early 1930s, the rate of death from sepsis after childbirth in the UK was 100-120 per 100,000 births, despite rigorous hygienic precautions. Within 10 years, following the introduction first of sulphonamides then of penicillin, this rate fell to almost zero [2]. The risk of abdominal surgery likewise has been reduced hugely; death resulting from appendicectomy is rare where once it was common. Antimicrobial agents have enabled interventions that were previously unthinkable, either because of the risk of wound contamination, or because they demand or cause immunosuppression, exposing the patient to infection by opportunist pathogens.

Unfortunately, the use of antibiotics exerts an inevitable Darwinian selection for resistance. Once selected, resistant bacteria can spread, or can transfer their resistance genes to other bacteria. The result has been erosion of antibiotic efficacy, putting the past half-century's medical progress at risk.

Until recently, man kept ahead. From 1945 to the late 1980s, new antimicrobial agents were developed faster than bacteria developed resistance. Gradually, though, a change occurred. While the 1950s and 1960s saw the discovery of numerous *new classes* of antimicrobial agents, the 1980s and 1990s yielded only improvements *within* classes. The pharmaceutical houses continued to screen new natural products (ie microbial extracts) for antimicrobial activity, but compounds suitable for development ceased to be found. Now, in the closing years of the century, there is an uneasy sense that micro-organisms are 'getting ahead' and that therapeutic options are narrowing.

In the UK low-grade opportunist pathogens (eg *Enterococcus* and *Acinetobacter* spp) resistant to all antibiotics are being seen, as are more virulent pathogens that are susceptible to only one or two compounds (eg *Staphylococcus aureus* susceptible only to glycopeptides and gram-negative rods susceptible only to carbapenems). The situation is worse in southern Europe, the Americas and East Asia. In Japan there are strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa* that are resistant to all established antibacterial agents, and susceptible only to experimental drugs or to those with poor pharmacological behaviour (ie poorly absorbed, or with unacceptable side-effects). There is every reason to fear that these pathogens will be imported to the UK, or will evolve independently here. Their spread threatens a return to darker times, when surgery was restricted to simple operations on the otherwise healthy, and when organ transplants, joint replacements and immunosuppressive therapies were unthinkable.

Resistance to antibiotics is not confined to hospitals, but is emerging in community pathogens. *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* have shown progressive declines in penicillin susceptibility, and have accumulated resistance to other antibacterial agents. The same processes are occurring in *Neisseria meningitidis*, albeit more slowly. Pneumococcal meningitis presents the worst case among community-acquired infections, with the advent of strains resistant to all of the antibacterial agents that have adequate penetration to the infection site. Multi-drug resistant *Mycobacterium tuberculosis* is another major concern, although less so in the UK than in developing countries. This evolution is occurring at a time when tuberculosis is undergoing a renaissance.

While most concern about antimicrobial resistance has focused on antibacterial

drugs, analagous problems are now arising with antifungal and antiviral agents. Resistance to azole antifungal agents has become a significant problem in several groups of patients [3]; likewise, resistance to antiviral agents is important in patients with human immunodeficiency virus (HIV) infection [4].

Even where resistance does not cause infections to become untreatable, it may add cost. The initial therapy must be replaced with agents that are (usually) more expensive and which may have undesirable side-effects. Thus, infection with methicillin-resistant *Staphylococcus aureus* (MRSA) must often be treated with vancomycin, a drug with poorer anti-staphylococcal activity and greater toxicity than oxacillins, to which these staphylococci are resistant. More generally, patients whose therapy proves inappropriate as a result of the presence of resistant bacteria are more likely to experience complications or to stay longer in hospital, adding to the cost. These points are illustrated in Figure 2, showing the incidence of various complications among surgical patients with peritonitis who received:

i)   *appropriate therapy, to which all pathogens were susceptible;*
ii)   *appropriate therapy following changes based on microbiological results;*
iii) *inappropriate therapy, where the patient continued to receive drugs to which one or more of the pathogens present was resistant.*

Re-operation, abscess formation and further infection were all commoner in those who received inappropriate therapy.

FIGURE 2   **COMPLICATIONS AFTER APPROPRIATE, CHANGED AND INAPPROPRIATE ANTIBACTERIAL THERAPY IN SURGICAL PATIENTS WITH PERITONITIS**
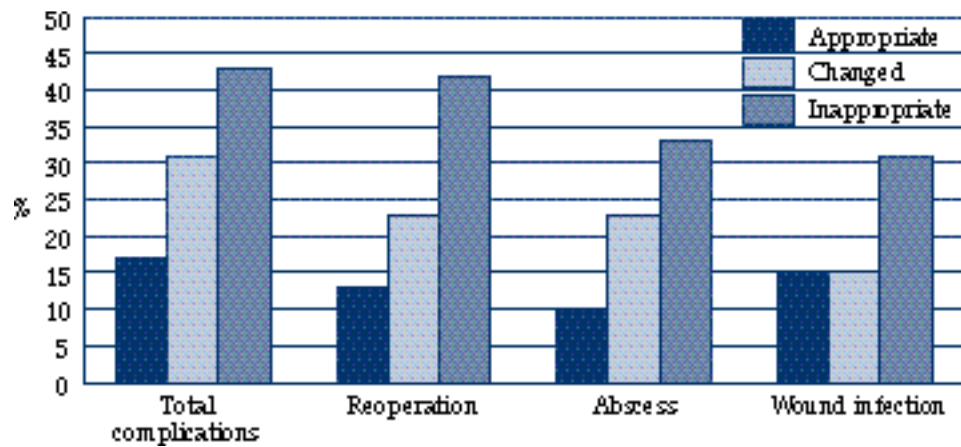
Data source: reference [5].

All microbes – bacteria, fungi, viruses and parasites – have the capacity to become resistant to the antimicrobial agents used for treatment. This resistance is a problem for prescribers, consumers and future consumers of these drugs. Antimicrobial resistance makes it more difficult to find the right medicine to treat a patient, adds to the costs of treatment, prolongs stay in hospital and causes ill health and inconvenience to the patient. Resistance is a problem for all of us: prescriber, carer, policy maker, manager, pharmaceutical manufacturer, consumer. All have a role to play in developing an effective response; the one thing no one can afford to be is resistant to change.

In brief, the threats to health posed by antimicrobial resistance are:

- **Multi-drug resistance may lead to some conditions becoming untreatable**
- **Resistance may lead to inappropriate empirical treatment being used and therefore to loss of time in critically ill patients**
- **Antimicrobial resistance may increase length of hospital stay, use of antimicrobial agents, morbidity, mortality and cost**
- **Alternative drugs, where they exist, may be more toxic, less effective, or more expensive**

This document reviews these problems, and their consequences, at several levels:

Case-studies explore the day-to-day prescribing problems faced by doctors. The decision whether or not to prescribe antimicrobial agents is often finely balanced. The patient may benefit, but the use may select resistance, worsening the prognosis for other patients.

The basis and impact of resistance are reviewed in detail. Aspects of the use and misuse of antimicrobial agents that exacerbate the problem are identified, together with strategies to slow the accumulation of resistance and conserve the usefulness of available antimicrobial agents.

Recommendations are made. These recognise that the decisions concerning the prescribing of antimicrobial agents are often complex, and are as much about minimising harm as they are about maximising benefit.

Methods for implementation of the recommendations are reviewed.

This Report does not attempt to address all the issues, or to make recommendations that will solve all the problems associated with the use of antimicrobial agents. Nevertheless, several key areas are identified where innovative approaches may lessen a problem that affects us all.

The evidence base. The Sub-Group commissioned an independent review of the evidence pertaining to the potential for limiting the spread of antimicrobial resistance with improvements in prescribing patterns. The results of this review are summarised in Section 20.

4 ANTIMICROBIAL AGENTS

In the UK, antibacterial agents for humans are prescription only medicines (POM), ie they can be obtained only with a prescription from a medical or dental practitioner. The antiviral agent aciclovir, and some antifungal agents including fluconazole and remedies for athlete's foot, can be obtained from a pharmacist without a prescription. Data on prescriptions for antimicrobial agents dispensed by pharmacists in the UK are shown in Table 1.

TABLE 1

THE NUMBER OF PRESCRIPTIONS (THOUSANDS) FOR ANTIMICROBIAL AGENTS DISPENSED IN ENGLAND: 1993-96

AGENT	1993	1994	1995	1996
Antibacterial (BNF 5.1)	47684.1	45798.1	49369.6	46648.5
Antifungal (BNF 5.2)	1172.8	1240.5	1280.1	1366.2
Antiviral (BNF 5.3)	176.9	212.4	225.3	245.6

ß-Lactam antibiotics currently account for about half of the antimicrobial agents used in humans, and this use has selected for bacteria resistant to ß-lactams. Most resistance is caused by ß-lactamases (enzymes that degrade ß-lactams). Two approaches have been used to overcome this resistance: ß-lactams can be modified so that they are not degraded by ß-lactamases, or can be combined with compounds that inhibit the activity of ß-lactamases.

Most other antimicrobial agents are more likely than ß-lactams to lose their antibacterial activity when their structure is modified. The two exceptions are aminoglycosides, where modifications have been useful for overcoming accumulated resistance, and fluoroquinolones, where modifications have increased their inherent activity several hundred-fold.

The terms 'antimicrobial agent' and antimicrobial' are used in this Report principally to encompass antibiotics (substances produced by micro-organisms that kill or inhibit other micro-organisms) and chemically produced antibacterial drugs, and also to include, where appropriate, antiviral and antifungal agents.

TABLE 2	THE MAJOR CLASSES OF ANTIBACTERIAL AGENTS AND THE SOURCES OF RESISTANCE

ANTIBACTERIAL CLASS AND MAJOR EXAMPLES	YEAR INTRODUCED	RESISTANCE STATUS
ß-LACTAMS		
Penicillins susceptible to ß-lactamases penicillin G penicillin V ampicillin amoxycillin ticarcillin piperacillin	1944	Much resistance has accumulated, due largely to ß-lactamases. Some resistance overcome by protecting with ß-lactamase inhibitors. No new penicillin for 15 years
Penicillins resistant to ß-lactamases methicillin flucloxacillin	1960	Used to treat staphylococcal infections, but methicillin-resistant *Staphylococcus aureus* (MRSA) are not sensitive and are increasing
Penicillin combined with an inhibitor amoxycillin/clavulanate piperacillin/tazobactam	1976	ß-Lactamases are the main cause of resistance to ß-lactams, especially penicillins. Inhibitors overcome some, but not all this resistance
Cephalosporins (generation) cephalexin (1st) cefuroxime (2nd) cefotaxime (3rd) ceftazidime (3rd) cefpirome (4th)	1962	Huge family. Successive 'generations' were developed to overcome resistance to previous generations. Resistance is now accumulating to third-generation drugs, and this resistance is only partly overcome by the newest fourth-generation drugs
Carbapenems meropenem imipenem	1975	These are the most powerful ß-lactams, and they can be used to treat infections caused by many gram-negative bacteria that are resistant to cephalosporins. Resistance is emerging in *Acinetobacter* spp and *Pseudomonas aeruginosa*

OTHER MAJOR ANTIMICROBIAL CLASSES		
CLASS AND MAJOR EXAMPLES	**YEAR INTRODUCED**	**RESISTANCE STATUS**
Glycopeptides vancomycin teicoplanin	1956	These are the 'drugs of last resort' for treating infections caused by staphylococci, streptococci and enterococci that are resistant to all other antibacterial agents. Resistance was thought to be impossible, but has emerged and spread in enterococci. Intermediate resistance has been observed in MRSAin Japan and the USA. Loss of activity against MRSAwould have disastrous consequences for public health

OTHER MAJOR ANTIMICROBIAL CLASSES CONTINUED		
Aminoglycosides streptomycin gentamicin amikacin	1947	Used to treat infections caused by gram-negative opportunist organisms. Resistance is rare in the UK, but is commoner elsewhere. Aminoglycosides are toxic to humans and serum levels must be monitored carefully. No new analogues have been introduced since the early 1970s
Fluoroquinolones ciprofloxacin norfloxacin	1982	Derivatives of nalidixic acid. They have good activity against gram-negative bacteria, but resistance is now emerging in opportunist organisms acquired in hospital and in salmonellae. Resistance is common in MRSA. New derivatives are being developed, but they have reduced activity against bacteria with acquired resistance to older analogues
Macrolides erythromycin azithromycin clarithromycin roxithromycin	1952	These are used mainly in primary care to treat respiratory tract infections. Resistance is widespread in *Streptococcus pneumoniae.* Newer analogues cause less severe gastrointestinal upset and azithromycin is effective against *Haemophilus influenzae.* However, new analogues are not active against staphylococci, streptococci or pneumococci that are resistant to erythromycin
Trimethoprim	1970	Used mainly to treat urinary tract infections which are mostly caused by *Escherichia coli.* Resistance is common. No new analogues
Tetracyclines oxytetracycline	1953	Used to treat infections caused by a wide range of organisms, but their use is decreasing because resistance has become frequent in many organisms. New analogues (glycylcyclines) overcome this resistance, but there are problems in development
Chloramphenicol	1947	Can be used to treat a wide range of infections, but its use is discouraged because of its toxicity for man. No new analogues have been introduced since the 1950s
Fusidic acid	1962	Used to treat staphylococcal infections. Primary resistance is rare, but resistance due to mutation is acquired readily in clinical use. No new analogues have been introduced since the late 1960s
Mupirocin	1983	Used topically to treat the carriage of MRSA. Resistance is increasing. No new analogues
Metronidazole		Used to treat infections caused by anaerobic bacteria. Few reports of resistance, except with *Helicobacter pylori*
Rifampicin	1961	Used to treat infections caused by gram-positive bacteria and mycobacteria. Primary resistance is rare, but emerges readily by mutation during clinical use. No new analogues
Isoniazid **Ethambutol**		Used to treat tuberculosis. Resistance is rare in the UK, but commoner elsewhere. Most resistant cases in the UK have acquired their infection elsewhere

5 BASIS OF RESISTANCE

The great principle of antimicrobial resistance is 'Survival of the Fittest' [6]. Antibacterial agents kill susceptible bacteria, but resistant organisms survive to infect other patients. At the same time, advances in medicine enlarge the pool of patients who are so immunocompromised as to be susceptible to infection by organisms that historically were harmless, but which are adept at developing resistance. Resistance can arise via mutation, gene transfer or by the selection of inherently resistant species. The importance of these processes varies with the organism, the antimicrobial agent and the clinical setting.

5.1 MUTATION

Mutations are spontaneous genetic changes, arising randomly. They may confer resistance by various mechanisms (Figure 3), specifically:

i) *Increasing destruction of the antimicrobial agent*
ii) *Reducing drug uptake*
iii) *Increasing drug excretion*
iv) *Altering the antimicrobial agent's target so that it is no longer bound by the drug*
v) *Activating an alternative metabolic pathway that by-passes the target*

Bacteria can divide once every 20–30 minutes, so that overnight, one cell can yield one billion. Once a resistant mutant emerges, it may swiftly become the predominant bacterial population. In the worst case, resistant mutants may be selected in therapy, causing failure of treatment in the individual patient. Some drugs select resistant mutants from most species; others do so for particular pathogens. This aspect is expanded in Section 12.2.

FIGURE 3 MECHANISMS OF ANTIBACTERIAL RESISTANCE

The antibacterial agent, drawn as a bullet, heads towards its target. Resistance may arise: (i) if it is inactivated before it reaches this target; (ii) if the bacterial cell becomes impermeable, so that the target cannot be reached; (iii) if the cell acquires the ability to pump back out the antibiotic; (iv) if the target is altered so that it is no longer recognised by the antibacterial agent; or (v) if the bacterium acquires an alternative metabolic pathway, by-passing the antibacterial agent's site of action.
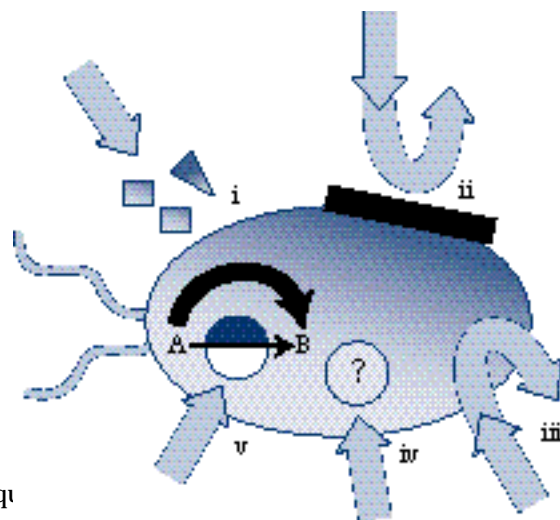
GENE TRANSFER

Bacteria can exchange genetic information (DNA) by several mechanisms. Most importantly, plasmids – loops of DNA separate from the chromosome – may carry resistance genes and can transfer from cell to cell. Within plasmids, resistance genes may lie on transposons, which are sticky-ended sections of DNA that can jump from plasmid to plasmid, and to the chromosome, increasing their dissemination (Figure 4). Individual plasmids may carry resistance genes, including those encoding antimicrobial agent-inactivating enzymes, target-modifying or by-passing enzymes and drug efflux pumps (Figure 3).

One example serves to show the consequences of plasmid-mediated resistance. The first broad-spectrum penicillin (ampicillin) was introduced in 1963 and initially had good activity against most gram-negative bacteria, including *Escherichia coli*, *Haemophilus influenzae* and *Neisseria gonorrhoeae*. In l965, however, ampicillin-resistant *Escherichia coli* were recorded, and found to have a plasmid-mediated ampicillin-degrading enzyme, dubbed 'TEM-1 ß-lactamase'. In the subsequent 33 years this enzyme has spread to 40–60% of isolates of *Escherichia coli* and closely related species, and has also reached *Haemophilus influenzae* and *Neisseria gonorrhoeae*, where it now occurs in 5–15% of UK isolates and in 30–50% of those from Southern Europe and South East Asia [7,8].

The origins of plasmid-mediated resistance are unclear. Plasmids existed before man used antimicrobial agents clinically and may once have encoded mostly metabolic traits [9]. Under huge selection pressure, plasmids have since recruited resistance genes from chromosomal sources, including antibiotic-producing bacteria, which must protect themselves against their products. Such 'escapes' are rare, but once a gene is on a plasmid, its potential for spread is huge.

There are other sources of 'foreign' DNA, besides plasmids. Resistance genes may insert directly in the bacterial chromosome, perhaps carried by bacteriophages (viruses that infect bacteria). A few species – *Streptococcus pneumoniae, Neisseria meningitidis* and *Neisseria gonorrhoeae* – can absorb DNA from dead resistant cells of related species and insert this into their own chromosomes. The resulting 'mosaic' genes can encode drug-resistant products [10].

FIGURE 4

PLASMIDS AND TRANSPOSONS: GENETIC MECHANISMS OF RESISTANCE TRANSFER

Plasmids are loops of DNA that may transfer among cells, spreading resistance.
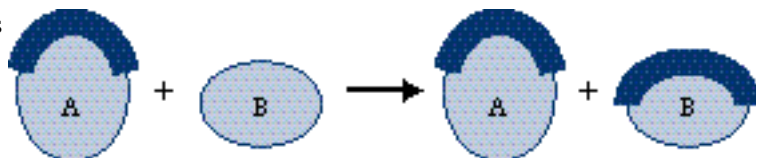
Transposons are sticky-ended DNAsections that jump between plasmids and the chromosome. Transposons may spread from relatively non-transmissible plasmids to transmissible ones. In the diagram the transposon (drawn as a thick line) jumps from the larger non-transferable plasmid (A) to the smaller readily transferable one (B).

5.3　INHERENTLY RESISTANT SPECIES

This is mostly a problem in hospitals, where there are many patients with underlying disease who are prone to infection by 'opportunist' bacteria.

If antibacterial agents are successful against one species, an ecological niche is created for others that are more resistant. Increased hospital use of cephalosporins and quinolones may lie behind the rise of enterococci (Section 10.2), which are naturally resistant to these drugs [11].

Species-by-species competition is less important in the community, where most infections are caused by classical pathogens, not opportunists; nevertheless, as in hospitals, antimicrobial chemotherapy may disrupt the normal bacterial flora, allowing overgrowth of undesirable bacteria (eg *Clostridium difficile*), yeasts and fungi. The commonest example is the development of candidal thrush following a course of antibiotic therapy.

5.4　MULTI-RESISTANCE

Resistances are often viewed individually, but the major problem is **multi-resistance.**

BOX 3　MULTI-RESISTANCE

Organisms resistant to one antibacterial agent are more likely than others to be resistant to unrelated agents. It is not the methicillin resistance of methicillin-resistant *Staphylococcus aureus* (MRSA) that matters; rather, that many MRSA are also resistant to most alternative drugs. Likewise, the vancomycin resistance of enterococci would not matter if enterococci were not already resistant to all other drugs.

The problem of multi-resistance is not confined to MRSA and enterococci. Table 3 compares resistance rates to unrelated drugs among penicillin-resistant and -susceptible *Streptococcus pneumoniae*. Table 4 compares resistance to unrelated drugs for cephalosporin-resistant and -susceptible klebsiellae. In both cases, organisms with the index resistance show a greater frequency of resistance to unrelated compounds.

Multi-resistance is sometimes explained by the presence of single plasmids encoding diverse mechanisms, or by efflux systems that pump out multiple drugs. Often, however, there is accumulation of independent resistances. Multi-resistance undermines rotation of antibacterial agents as an answer to resistance and complicates the design of antimicrobial policies, as bacteria resistant to the front-line agent are also likely to be more resistant to 'reserve' compounds.

TABLE 3	RESISTANCE TO OTHER ANTIBACTERIAL AGENTS IN *STREPTOCOCCUS PNEUMONIAE* SENSITIVE AND RESISTANT TO PENICILLIN: DATA FROM 10 EUROPEAN CENTRES

OTHER ANTIBACTERIAL AGENTS	% RESISTANCE WHEN PENICILLIN RESULT IS		
	Susceptible	Intermediate	Resistant
Erythromycin	6	26	30
Tetracycline (doxycycline)	5	33	41
Chloramphenicol	4	25	53
Ciprofloxacin	12	17	8
Co-trimoxazole	11	53	97

Data source: reference [12].

TABLE 4	RESISTANCE TO OTHER ANTIMICROBIAL AGENTS IN KLEBSIELLAE SUSCEPTIBLE AND RESISTANT TO CEPHALOSPORINS: DATA FROM A EUROPEAN STUDY

OTHER ANTIBACTERIAL AGENTS	% RESISTANCE WHEN CEPHALOSPORINS RESULT IS	
	Susceptible (ESBL negative) n = 675	Resistant (ESBL positive) n = 220
Gentamicin 1 mg/l	5.8	74
Amikacin 4 mg/l	1.1	52
Ciprofloxacin 1 mg/l	2.5	33

ESBL: extended spectrum ß-lactamase that causes resistance to cephalosporins.

n = number of isolates tested.

Data source: reference [13].

6 DOES USE OF ANTIMICROBIAL AGENTS CAUSE RESISTANCE?

The evidence that use of antimicrobial agents (whether human, veterinary or even horticultural, and whether appropriate or not) causes resistance is overwhelming, although mostly circumstantial.

The key facts are:

i) Acquired resistance is absent from bacteria ante-dating the antimicrobial era [9]. The only resistances seen in such organisms are those inherent to particular species.

ii) The introduction of new antimicrobial agents has been followed repeatedly by the emergence of resistance. The time scale has varied, reflecting the complexity of the evolution required for resistance, but the basic pattern is constant: resistance follows use.....

iii) The relationship between use and resistance is starkest when resistance is mutational and can be selected during therapy, causing clinical failure. This topic was reviewed by Fish *et al* [14]. Particular and frequent examples include:

- Cephalosporins – versus – *Enterobacter* and *Citrobacter* spp
- All antimicrobial agents (except perhaps meropenem) – versus – *Pseudomonas aeruginosa*
- Rifampicin and streptomycin – versus – Most species
- Quinolones and fusidic acid – versus – Staphylococci

In the case of ß-lactams versus *Enterobacter* species, there is concordance between the agents that select resistance *in vivo* and those that select *in vitro* [7,15].

iv) Individuals receiving antimicrobial therapy tend to develop a resistant commensal bacterial flora. If they develop a further infection, caused by an opportunist pathogen from within their own bacterial flora, it is consequently more likely to be resistant than in patients who had not received the prior therapy [15-18].

v) Resistance is greatest where use of antibacterial agents is heaviest. This applies at both national and clinical unit level, the clearest example being the excess of resistance in intensive care units compared with general hospital wards or out-patient clinics (Section 11.1) [15,17,19-21].

While exposure to antimicrobial agents is the major factor in selecting resistance, other contributors cannot be dismissed. Plasmids may also confer resistance to disinfectants – notably quaternary ammonium compounds – and to mercury, as well as to systemic antimicrobial agents. Thus the use of disinfectants and, controversially, the presence of amalgam dental fillings (which slowly release mercury) may conserve plasmids that also determine antimicrobial resistance [22].

TO PRESCRIBE OR NOT TO PRESCRIBE?

Microbial pathogens are increasingly resistant to the available drugs. However, the anxious parent and the unwell adult continue to expect a prescription of a 'pill to cure their ill'. GPs, hospital physicians, surgeons, paediatricians or obstetricians continue to prescribe antibiotics, sometimes for inappropriate indications, in inappropriate doses, for inappropriate lengths of time. Why is this so, and how can it be changed?

BOX 4	THE ANTIMICROBIAL TUG OF WAR
What stimulates prescribing ?	**What inhibits prescribing ?**
Prescribers Failing to prescribe may lead to clinical complications or litigation Applying rules learned as a student which may no longer be appropriate 'Clinical judgement' Scientific and promotional literature A prescription is an easy way to end a consultation	**Prescribers** Advice from specialists in microbiology and infectious disease, who discourage excessive prescribing Good basic training on risks and benefits
Patients Patients' expectations drive prescribing Many patients expect a 'script' Belief that they need an antibiotic to stop a cold 'going to their chest' Anxiety over sick children	**Patients** Some patients are averse to prescription and seek reassurance that they will recover without an antibiotic
Nurses May not fully appreciate the risks associated with inappropriate use of antimicrobials	**Nurses** See the problems associated with over-prescription, resistance, ward closures, antibiotic-associated diarrhoea and try to educate prescribing colleagues and patients
Pharmacists Often first community contact; may advise that a prescription is necessary	**Pharmacists** Particularly in hospitals, have an important role in controlling prescribing and identifying inappropriate prescribing
Pharmaceutical industry Wants to sell its products	**Pharmaceutical industry** Wants to ensure long product life

This is the antimicrobial tug of war, and what is required is action that will ensure that every prescription is justified, is of the appropriate drug, dose and regimen, and is reassessed in the light of clinical response and microbiological results, if necessary.

BOX 5	**THE PAINFUL EAR**

The parent, kept awake by a distressed unhappy child with a painful ear, wants their child cured and their anxiety relieved.

Acute otitis media (AOM – infection of the middle ear) is a common condition of childhood. A child with AOM is distressed, unhappy and febrile. The parents will be concerned and eager for something to be done. Many patients expect a prescription if they go to the GP and are not content if they do not receive one. The GP may feel under pressure from the family and may not have the time needed to explain why the child does not need an antibiotic; it is easier to write the prescription. When the patient improves it is attributed to the antibiotic, reinforcing the cycle of expectation. A GP will see numerous children with AOM each year [23] and most will receive an antibiotic [24].

Much has been written on the treatment of AOM, although, as with many trials of antibiotics, not all are methodologically sound [25]. A recent *Drug and Therapeutics Bulletin* [26] suggested that antibiotics improved symptoms in the short term and shortened the course of disease, albeit at the cost of unwanted effects in one child out of five. However, this was not a formal review of the literature.

Meta-analyses of randomised controlled studies show that the benefit of routine antibiotic use for AOM is unproven [24,27], or modest [28]. One overview [28] suggested that children treated with antibiotics were less likely to have pain 2–7 days after presentation, but the benefit was small and 17 children must be treated early for one to benefit, whilst the other 16 run the risk of unnecessary antibiotics without any benefit. Unfortunately, it is difficult to predict which child will benefit. Countries with lower rates of antibiotic prescribing for AOM **do not** have any increase in the number of complications [27].

Even if antibiotics are prescribed, there is debate about the appropriate duration of treatment; the optimum length is uncertain, but 3- and 10-day courses were equally effective in one study [29].

Faced with the evidence from the literature:

The parent might decide that the slight chance of less pain 2–7 days after presentation is a good reason for pressing for an antibiotic for their child (even if they agreed that it would be better if other children did not have inappropriate prescriptions).

The GP may be confused as to whether the balance of evidence is in favour of, or against, the prescription of antibiotics.

CONCLUSION

Antibiotics are probably unnecessary in AOM. Reassurance, time and adequate pain relief are required. If antibiotics are prescribed, then the course should be limited to 3 days.

The unnecessary prescription and consumption of antibiotics is everyone's responsibility.

Effective treatment of infectious disease can only be preserved through a determination on the part of policy makers, prescribers, consumers and manufacturers to minimise unnecessary consumption. Whilst there may be difficult clinical decisions, as exemplified in Boxes 5–8, there are also circumstances when it is

clear that prescription of an antibiotic is wrong. A patient with coryza (the common cold) should not receive an antibiotic and women with uncomplicated urinary tract infections should not receive antibiotics for more than 3 days.

Prescription of an antibiotic should be seen as a serious step, similar to the prescription of steroids or any other potentially hazardous medicament.

| BOX 6 | THE SORE THROAT |

THE SORE THROAT

Sore throats are common, particularly in children. Most are viral, do not require treatment with antibiotics and can be left to run their course. Recurrence and relapse are more common in those who have had early treatment with antibiotics [30].

Nevertheless, the GP may be under considerable pressure to prescribe an antibiotic. A recent study showed that patients were more likely to leave the consultation satisfied if they had received a prescription; however, they were no more likely to be satisfied at the end of the illness. Those who received antibiotics were more likely to return to the doctor for treatment in future attacks and were more likely to believe in the efficacy of antibiotics. A similar study in general practice of prescribing for patients with acute lower respiratory illness showed that patient pressure again was a significant factor in the prescription of an antibiotic when the clinical indication was doubtful.

A minority of sore throats are caused by a bacterium, *Streptococcus pyogenes*, which can produce a local abscess, or, rarely, kidney problems and rheumatic fever. It is not easy to distinguish a streptococcal sore throat from a sore throat caused by viral infection. Therefore, many doctors prescribe antibiotics for a sore throat with the intention of preventing the consequences of infection due to *Streptococcus pyogenes*.

CONCLUSION

Sore throats should not be treated with antibiotics, unless there is good evidence that they are caused by *Streptococcus pyogenes*.

| BOX 7 | SINUSITIS |

SINUSITIS

Several studies, some of them randomised controlled trials, have shown antibiotics to be effective in the treatment of proven acute sinusitis [31–33]. Most of these studies have used 10-day courses of antibiotics. One comparative study showed that 3-day courses of antibiotics were as effective as treatment for 10 days [34].

Recent overviews of the treatment of acute sinusitis-like symptoms in adults in primary care have suggested that there is no benefit from antibiotic treatment [35–38].

CONCLUSION

The adult with sinusitis-like symptoms in primary care does not need immediate antibiotics. In proven acute sinusitis 3 days of antibiotic therapy are as effective as 10 days.

| BOX 8 | CYSTITIS (URINARY TRACT INFECTION) |

Cystitis is common in women. Each year about one woman in 20 will present to her GP with symptoms suggestive of cystitis; about half of these women will have an infection (defined by the presence of a significant number of bacteria in their urine). Most infections occur in otherwise healthy women and are caused by coliform bacteria. Those women with symptoms in the absence of bacterial infection have the urethral syndrome and are unlikely to benefit from antibiotics [39,40].

In otherwise healthy adult women there is no need to culture the urine. The presence of an infective cause of the symptoms can be established by the history, clinical signs and results of urine dipstick testing. The dipstick tests for the products of bacterial metabolism (the conversion of nitrates to nitrites) or the presence of pus cells (leucocyte esterase test) [41]. Urine culture should be undertaken in pregnancy, in non-pregnant women when empirical treatment has failed, in those with clinical evidence of pyelonephritis, when there are anatomical defects of the urinary tract and when there are other complications.

Uncomplicated cystitis can be treated empirically with trimethoprim. Where resistance is common, the local medical microbiologist will be able to advise as to an appropriate alternative. Several studies have shown that a 3-day course of treatment is as effective as a 5- or 7-day course [42–46]. The use of 3-day treatment has been recommended in a recent *Drug and Therapeutics Bulletin* [47].

Symptoms can be relieved through general measures – drinking more, analgesia and alkalinising the urine. Symptoms may persist for a short while even following effective antimicrobial therapy, as the inflammation may take time to resolve. If there is doubt about successful empirical therapy, a urine culture should be performed.

CONCLUSION

Limiting the prescription of antibiotics for uncomplicated cystitis in otherwise healthy women to 3 days reduces the selection pressure for resistance.

WHERE ARE ANTIMICROBIAL AGENTS USED?

KEY POINTS

50% of antibiotic use in the UK is in man, 50% in animals

80% of human use is in the community

50% of human community use is in respiratory tract infections, 15% in urinary tract infections

Considerable local and regional variation exists in prescribing

In hospitals, antimicrobial agents account for 10–30% of the drugs budget

Accepting that usage of antimicrobial agents promotes resistance, and that one key to mitigating the problem is to reduce usage, it is vital to identify where usage occurs. In the UK, about 50% of usage is in man and about 50% in veterinary medicine or for growth promotion in animals. Of the human usage, 80% (by weight) is in the community and 20% in hospitals.

It should be added that usage in the UK is relatively low in international terms and mostly of cheaper, older antimicrobial agents. The USA, with a population of 300 million, accounts for about 50% of the world market in antimicrobial agents; Japan, with 130 million, for 25%; Italy, with 55 million, for 5%; and the UK, with 60 million, for 2%.

8.1	COMMUNITY PRESCRIBING

Most antibiotic prescribing in the UK (80%) is for oral antibiotics in the community. About 50 million antibiotic prescriptions are dispensed in England every year – an average of one prescription per person per year. About half of this community use is for respiratory tract infection (RTI), with a further one-sixth for urinary tract infection (UTI) (Table 5). This prescribing is mostly carried out by GPs, but dentists account for about 7% of community prescriptions.

Further data on usage of antimicrobial agents in the community were generously provided by IMS HEALTH from their M*ediplus*® UK Primary Care Database (UKPCD) which is based on a panel of 139 practices comprising 565 GPs. From 1995 to 1997, there were 221,000–222,000 prescriptions per annum for amoxycillin and its analogues (ampicillin, bacampicillin and pivampicillin) in this panel of practices. These give a projected total of over 13 million prescriptions per year, when scaled up for the national total of 36,200 GPs. Twenty-eight of the top 30 reasons cited for prescribing amoxycillin and its analogues in 1997 related to respiratory symptoms, and these included all the top 15 reasons for prescribing these agents. Expressed another way, respiratory symptoms accounted for over 70% of prescribing of amoxycillin and its analogues, or over 9 million community prescriptions per annum.

Community prescribing of the fluoroquinolone ciprofloxacin was also reviewed. Ciprofloxacin is the most heavily prescribed fluoroquinolone, accounting for 84% of all community prescribing in this class of antibacterial agents (IMS HEALTH Maxims Database); moreover, the fluoroquinolones are the most powerful antibacterial agents to be used at a significant level in the community.

There were 11,857 ciprofloxacin prescriptions in the 139 survey practices in 1995, rising to 14,056 in 1997; these figures project to national totals of 760,000 prescriptions in 1995 and 900,500 in 1997. In 1997, the commonest single reason for prescribing ciprofloxacin was urinary tract infection. However, 40% of community ciprofloxacin prescriptions were for respiratory symptoms. This is surprising, as ciprofloxacin is more appropriate against urinary pathogens, and has only borderline activity at a standard dosage against *Streptococcus pneumoniae*, which is the most serious common respiratory pathogen in the community. It may be that ciprofloxacin was used as a second-line agent in unresponsive respiratory infections, but heavy primary usage in this milieu would be disturbing.

FIGURE 5

ANTI-INFECTIVE ITEMS PRESCRIBED PER PERSON FOR HEALTH DISTRICTS AND REGIONS, 1996–97
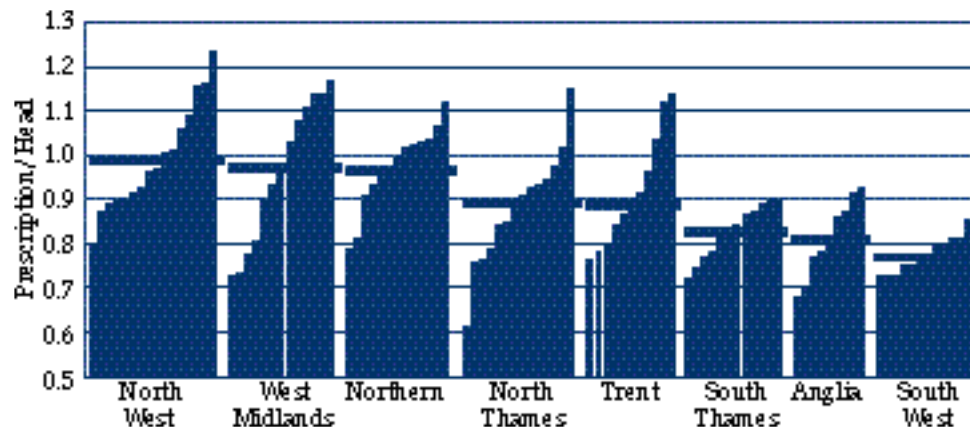
Usage is subject to considerable variation, Figure 5 shows antimicrobial prescribing by Health Region in England and Wales in 1996–97. The horizontal bar represents the value for a whole Region; Districts are grouped by Region. Variation is approximately two-fold between the districts with the lowest and highest prescribing. There is some suggestion that prescribing is higher in the north than the south and in poorer areas than richer, but the relationships are equivocal.

8.2

PRESCRIBING IN HOSPITALS

Although hospital prescribing accounts for only 20% of human usage and 10% of all use (human plus veterinary), it is of key importance because it is concentrated, and because hospitals – with high populations of immunocompromised patients – are fertile breeding grounds for opportunist bacteria that are adept at accumulating resistance. Furthermore, many of the parenteral antibiotics used in hospitals are considerably more expensive than the oral agents used in the community.

Audits at a teaching hospital trust showed that 20–25% of patients had received an antibiotic within the previous 24 hours, with a range of 40–50% in intensive care units down to under 10% in ENT surgery. As in the community, the bulk of prescribing was for respiratory tract infections (Figure 6).

FIGURE 6

USE OF ANTIMICROBIAL AGENTS IN A TEACHING HOSPITAL TRUST
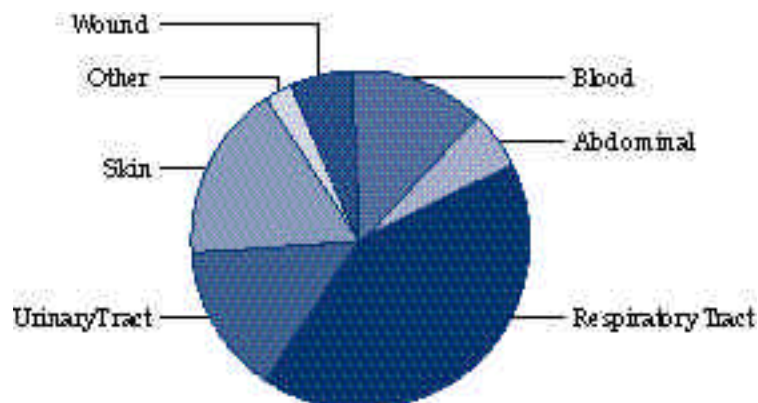
TABLE 5

TOTAL USE OF SYSTEMIC ANTIMICROBIAL AGENTS IN THE THE COMMUNITY AND HOSPITALS IN THE UK

ANTIMICROBIAL AGENTS	TOTAL (kg)	TOTAL UK RETAIL (COMMUNITY) (1 year to Feb 1998)	TOTAL UK HOSPITAL (1 year to Jan 1998)
Systemic antibiotics*	**469,700**	**388,600**	**81,070**
Broad-spectrum penicillins	185,963	160,406	25,556
Medium/narrow-spectrum penicillins	76,900	59,800	17,200
Cephalosporins + combinations	51,000	35,900	15,100
Other β-lactams (excluding penicillins, cephalosporins)	536	9	527
Fluoroquinolones	13,900	10,300	3600
Nalidixic acid	647	588	59
Aminoglycosides	5400	109	5300
Tetracyclines + combinations	47,500	45,900	1600
Trimethoprim combinations	14,400	10,900	3500
Fusidic acid	808	354	454
Glycopeptides	503	9	493
Chloramphenicol + combinations	113	25	88
Rifampicin/rifamycin	27	12	14
Nitrofurantoin	787	742	45
Fosfomycin	15	14	1
Spectinomycin	2	1	1

*Total excludes minor items not listed separately in the table.
Data kindly provided by IMS HEALTH, Maxims Database.

FIGURE 7

THE PYRAMIDS OF ANTIMICROBIAL USE AND SELECTION FOR ANTIMICROBIAL RESISTANCE

Most prescribing of antimicrobials (80%) takes place in the community; 20% of prescribing is for small numbers of patients, often in specialised hospital units. Both intense pressure in a small number of hospitalised patients and less intense selection pressure in large numbers of patients in the community cause problems with resistance.

9

THE EXTENT OF BACTERIAL RESISTANCE IN THE UK

TABLE 6

BACTERIAL RESISTANCE IN THE UK

	Penicillins	Cephalosporins	Carbapenems	Tetracycline	Chloramphenicol	Aminoglycosides	Quinolones	Trimethoprim	Fusidic acid	Erythromycin	Glycopeptides	Rifampicin	Ethambutol & isoniazid
S. aureus MethS	●	○	○	✪	✪	✪	✪	✪	✪!	●	○	✪!	–
MRSA	●	●	●	✪	●	●	●	●	✪!	●	○	✪!	–
Enterococci	✪	–	✪	●	●	●	–	●	–	●	✪	–	–
β-haem. streps	○	○	○	✪	✪	–	–	✪	–	✪	○	✪	–
S. pneumoniae	✪	✪	○	✪	✪	–	–	–	–	✪	○	✪!	–
Viridans streps	✪	✪	○	✪	✪	●	–	●	–	✪	○	✪!	–
E. coli	●	✪	○	●	●	✪	✪	●	–	–	–	–	–
Klebsiella spp	–	✪	○	●	●	✪	✪	●	–	–	–	–	–
Enterobacter	●	●!	○	●	●	✪	✪	●	–	–	–	–	–
Pseudomonas	✪!	✪!	✪!	–	–	✪!	✪!	–	–	–	–	–	–
Acinetobacter	●	●	✪	●	●	●	✪	–	–	–	–	–	–
N. meningitidis	○	○	○	○	●	–	○	✪	–	–	–	✪	–
N. gonorrhoeae	✪	○	○	✪	○	–	✪	✪	–	✪	–	✪	–
H. influenzae	✪	✪	✪	✪	✪	–	✪	✪	–	–	–	–	–
M. tuberculosis	–	–	–	–	–	–	–	–	–	–	–	✪	✪

– Inherently resistant.

✪ Acquired resistance in <20% of isolates.

● Acquired resistance in >20% of isolates.

○ Acquired resistance unknown, or virtually so.

! Resistance emerges readily by mutation.

NB: This table has many simplifications and ignores variation within antimicrobial classes. It aims to give only an overall, broad-brush picture.

10

CURRENT RESISTANCE PROBLEMS IN THE UK AND WORLD-WIDE

10.1 METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

The organism causing the greatest concern in the UK as regards antibiotic resistance is methicillin-resistant *Staphylococcus aureus* (MRSA).

Staphylococcus aureus is a classical wound pathogen, able to cause trivial or deep-seated disease. It is carried as a skin commensal by c. 30% of the population, usually in moist sites, such as the nose, perineum and axillae, and can survive for long periods on drier surfaces, including hands and medical equipment. These factors, together with a strong ability to accumulate multiple resistances, make *Staphylococcus aureus* a highly successful and adaptable pathogen.

When penicillin was introduced in l944 over 95% of *Staphylococcus aureus* isolates were susceptible, but this proportion has since shrunk to 10%. In the l950s, isolates resistant to penicillin and tetracycline became a major hospital problem. The introduction of ß-lactamase-stable penicillins (eg methicillin, flucloxacillin) in the early l960s overcame this problem, but was swiftly followed by the emergence of the first MRSA. These MRSA did not rapidly become prevalent, perhaps because another effective antimicrobial – gentamicin – entered use. However, by the late l970s, gentamicin-resistant MRSA had emerged; subsequently a series of epidemic MRSA (EMRSA) strains have evolved and spread. These are consistently susceptible only to the glycopeptides, vancomycin and teicoplanin. Many MRSA isolates also appear to be susceptible to fusidic acid, rifampicin and/or (decreasingly) ciprofloxacin, but mutational resistance is prone to emerge if these agents are used for therapy.

Recently there have been reports – first from Japan, then the USA, and most recently France – of MRSA with intermediate resistance to vancomycin and teicoplanin [48-50].These VISA (vancomycin-intermediate *Staphylococcus aureus*) are resistant to all available antibacterial agents and, unlike other organisms where pan-resistance is seen, have considerable pathogenicity for patients who are not already severely immunocompromised.

Staff or fellow patients colonised with MRSA pose an infection hazard to others with whom they are in contact; topical therapy with mupirocin is, therefore, widely used to eliminate carriage. When this compound was introduced in 1983, *Staphylococcus aureus* isolates were universally susceptible, but low- and high-level forms of resistance have since emerged. Low-level resistance is frequent [51] and is easily dismissed, as it is not associated with clinical failure. Nevertheless, it is increasing, suggesting that it benefits the bacterium [52]. High-level resistance is also increasing and leads to treatment failure [53].

The MRSA problem is primarily one of hospital cross-infection rather than repeated evolution of resistance [1]. Spread is aided where – as increasingly happens – patients are moved from ward to ward, or between hospitals and nursing homes. Effective control, as achieved and maintained in the Netherlands and Scandinavia, has depended on:

i)   *identification and treatment of carriers*
ii)   *isolation or cohorting of those with MRSA infection*
iii) *strict hygiene policies within hospitals*

10.1.1   MRSA IN THE UK AND INTERNATIONALLY

In recent years there has been a remarkable increase in MRSAin England and Wales. Much of the increase has reflected the spread of two strains, EMRSA15 and 16, which account for an increasing proportion of all MRSAsubmitted to the PHLS for typing.

Each year approximately 200 laboratories in England and Wales report susceptibility data for isolates from blood and CSF. The proportion of *Staphylococcus aureus* isolates resistant to methicillin remained at about 1.5% during 1989–91, but then increased to 13.2% in 1995, 21.1% in 1996 and 31.7% in 1997 (Figure 8). Simultaneously, there were significant increases in resistance to erythromycin (from 7.5% in 1989 to 18.7% in 1995), gentamicin (from 2.5% in 1989 to 5.3% in 1995) and ciprofloxacin (from 2.9% in 1989 to 23.1% in 1995). Rates of multi-resistance to these unrelated drugs were much higher among MRSAthan among methicillin-sensitive isolates.

FIGURE 8

PROPORTION (%) OF *STAPHYLOCOCCUS AUREUS* ISOLATES FROM BLOOD AND CSF THAT WERE RESISTANT TO METHICILLIN, 1989–97
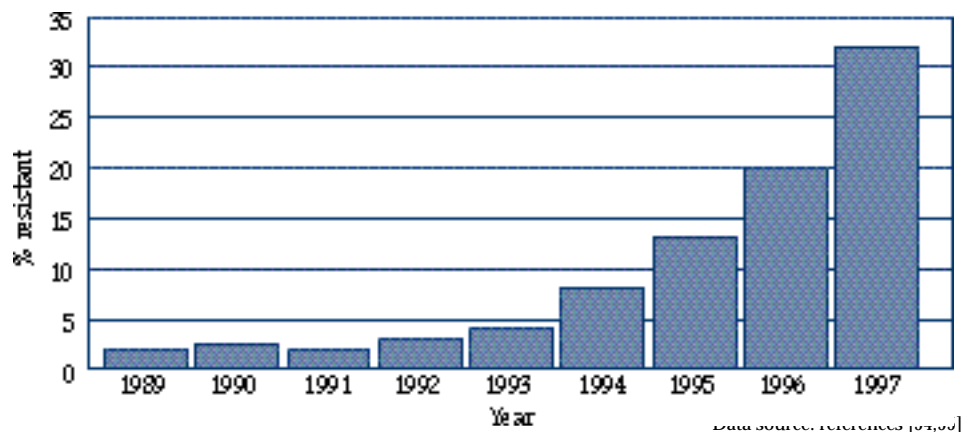
MRSArates around the world are summarised in Table 7. In general, they are lowest in those countries that have strict control of infection policies and highest in those that have liberal policies. The rates are distorted by the facts that MRSAstrains are clonal in origin and that different strains are prevalent in different parts of the world; some of these may be more adept than others at spreading between patients.

TABLE 7

INCIDENCE OF MRSA IN DIFFERENT PARTS OF THE WORLD

COUNTRY OF ORIGIN	% MRSA*
Scandinavia, the Netherlands	<1
USA	28
UK	32
Belgium	40
Japan, Korea	70

*MRSAas a percentage of all isolates of *Staphylococcus aureus.*

| 10.2 | ENTEROCOCCI |

Enterococci are a part of the normal human gut bacterial flora, where they are harmless. They have low virulence but can cause infection in patients whose resistance is impaired, particularly in specialised hospital settings such as renal dialysis and bone marrow transplant units. If they reach normally sterile sites in a vulnerable patient, enterococci can cause many types of clinical problem, from superficial infection of wounds and the urinary tract through to septicaemia and endocarditis. Serious infections are extremely difficult to treat, because of the degree of antibacterial resistance.

Enterococci are intrinsically resistant to available quinolones and cephalosporins. Increasing clinical use of these agents is a major reason for the rising importance of enterococci. In addition, enterococci readily gain resistance to other antibacterial agents, usually by acquisition of plasmids or transposons [11]. Most enterococci isolated from hospital patients in the UK are now resistant to tetracyclines, macrolides, chloramphenicol and trimethoprim. Combinations of penicillin and aminoglycosides were the mainstay of therapy until the mid-1980s, but high-level aminoglycoside resistance then emerged and spread; moreover, *Enterococcus faecium* (which is inherently resistant to penicillins) became more prevalent, leaving glycopeptides (vancomycin and teicoplanin) as the only agents to which sensitivity could be assumed. Unfortunately, glycopeptide resistance emerged in the UK in 1987, and has since spread to many hospitals. Many glycopeptide-resistant enterococci (GRE), particularly *Enterococcus faecium*, are resistant to *all* established antibacterial agents, forcing clinicians to use untested agents or combinations, with no guarantee of success.

Two forms of glycopeptide resistance occur, VanA and VanB, both coded by transferable plasmids. VanA exists in many countries, and the potential for its transfer to more pathogenic species, especially MRSA, is of great concern. This transfer, which would have catastrophic public health consequences, has been demonstrated in the laboratory, but not yet in the clinic [56].

10.2.1 MULTI-DRUG-RESISTANT ENTEROCOCCI (GRE) IN THE UK AND INTERNATIONALLY

Central comprehensive data on GRE infections are not collected by the PHLS, but epidemiological data are compiled for isolates submitted voluntarily. From 1987 to August 1996, the PHLS Antibiotic Reference Unit received GRE from over 1100 patients in 93 English and Welsh hospitals. Most (88%) had the VanA resistance type. From l987 to 1996, there was a rising trend in the number of hospitals submitting GRE (Figure 9). These establishments ranged from teaching centres to district general hospitals. Most referred only sporadic isolates, but outbreaks were investigated at 25 hospitals, with GRE becoming endemic at several. The epidemiology involved the spread of strains among patients and the spread of resistance genes among strains [57].

FIGURE 9

NUMBER OF HOSPITALS SUBMITTING ENTEROCOCI RESISTANT TO GLYCOPEPTIDES TO THE PHLS ANTIBIOTIC REFERENCE UNIT: ENGLAND AND WALES, 1987–96
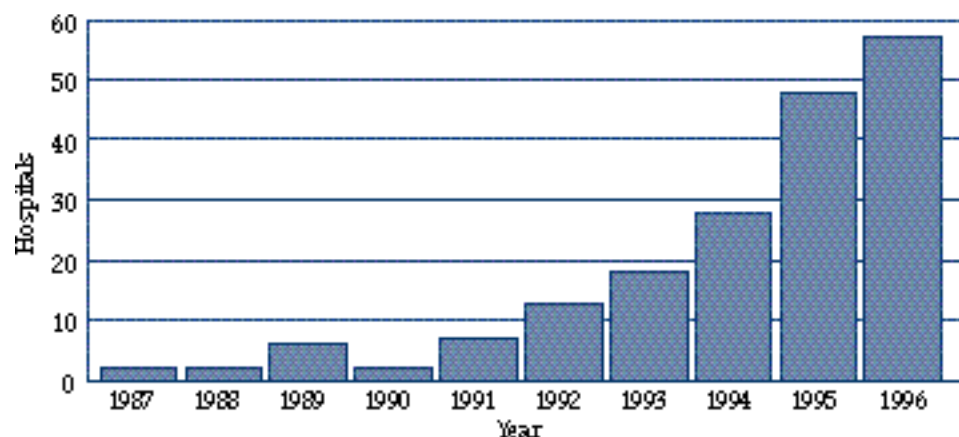
Data source: PHLS Antibiotic Reference Unit, data on file.

Few other countries have published national rates of GRE infection. Nevertheless, GRE are reported from an increasing number of countries and, in 1996, were reported for the first time from Sweden and Australia, and the first hospital outbreaks occurred in Germany, Italy and Canada. In the USA, the percentage of states within the National Nosocomial Infections Surveillance System which had hospitals reporting more than one GRE increased from eight (27%) out of 30 in 1989–93 to 16 (44%) out of 36 in 1994–95. Among nosocomial enterococci causing infection, the percentage resistant to vancomycin increased from 0.4% to over 10% between 1989 and 1995 [58].

10.3 STREPTOCOCCUS PNEUMONIAE

Streptococcus pneumoniae is most important as a cause of community-acquired pneumonia, which may also lead to bacteraemia. The organism is also a frequent cause of otitis media, particularly among children, and is the second most common cause of bacterial meningitis.

10.3.1 RESISTANCE TO ANTIBACTERIAL AGENTS

Historically, *Streptococcus pneumoniae* was exquisitely susceptible to penicillin, which could be used in most pneumococcal infections, including meningitis (where drug delivery is difficult). Macrolides (eg erythromycin), tetracyclines and co-trimoxazole were alternatives in respiratory tract infection, whereas several cephalosporins and meropenem were – and are – alternatives in meningitis.

Streptococcus pneumoniae strains with low-level penicillin resistance were recorded in the late l960s and those with high-level resistance began to appear in the late l970s. Strains with low-level resistance still respond to penicillin in respiratory tract infections and bacteraemia, but not in meningitis. Strains with high-level penicillin resistance may still respond to high-dose penicillin in the respiratory tract but, with MICs (minimum inhibitory concentrations – the lowest drug levels to stop the bacteria from growing) of 8 mg/l now being recorded for the most resistant isolates, there is little doubt that the 'border of the possible' is close. Strains with high-level penicillin resistance are often barely susceptible to cephalosporins in meningitis, and these drugs may need combination with vancomycin, which penetrates poorly at this site.

Crowded conditions (eg day-care centres, hospitals, military barracks and prisons) and prior therapy with ß-lactam antibiotics predispose to colonisation and disease with penicillin-resistant strains. Control will require innovative methods to reduce the selective pressure that results from widespread antimicrobial use and, most importantly, the development of effective vaccines that are immunogenic in young infants [59]. Vaccines are the **best** answer.

10.3.2   RESISTANCE IN THE UK

All *Streptococcus pneumoniae* isolated at each of the 53 Public Health Laboratories in England and Wales were sent to the Antibiotic Reference Unit during 2-week periods in March 1990 and March 1995. Rates of resistance to penicillin and erythromycin had increased over the 5-year interval, but resistance to rifampicin and vancomycin was not detected in either survey (Table 8).

Increasing prevalence of resistance to penicillin and erythromycin was also apparent when reviewing the collated results of susceptibility tests for *Streptococcus pneumoniae* isolates from blood culture or CSF in hospitals throughout England and Wales: penicillin resistance increased gradually but consistently from 0.3% in 1989 to 7.5% in 1997; resistance to erythromycin increased from 3.3% to 11.8% over the same period (Table 9) [60].

| **TABLE 8** | **PREVALENCE OF RESISTANCE TO ANTIBACTERIAL AGENTS IN *STREPTOCOCCUS PNEUMONIAE*: ENGLAND AND WALES** |

ANTIBACTERIAL AGENT	**PREVALENCE (%) OF RESISTANCE**	
	1990	**1995**
Penicillin G	1.5	3.9
Erythromycin	2.8	8.6
Tetracycline	5.0	5.1
Vancomycin	0	0
Rifampicin	0	0

Data source: reference [60].

| **TABLE 9** | **PREVALENCE OF RESISTANCE TO PENICILLIN G AND ERYTHROMYCIN IN *STREPTOCOCCUS PNEUMONIAE* ISOLATES FROM BLOOD AND CSF: ENGLAND AND WALES, 1989–95** |

YEAR	**PREVALENCE (%) OF RESISTANCE**	
	PENICILLIN G	**ERYTHROMYCIN**
1989	0.3	3.3
1990	0.5	5.1
1991	0.7	6.4
1992	1.9	8.6
1993	1.7	10.8
1994	2.5	11.2
1995	2.9	10.9
1996	3.7	9.9
1997	7.5	11.8

Data source: reference [60].

As already noted (Table 3) multi-resistance is a problem in that *Streptococcus pneumoniae* penicillin-resistant isolates are more likely than others to be cross-resistant to alternative drugs. Of 1751 penicillin-resistant *Streptococcus pneumoniae* tested by the PHLS Antibiotic Reference Unit between 1993 and 1995, 36% were resistant to erythromycin, and many were also resistant to tetracycline and/or chloramphenicol [data on file; PHLS].

10.3.3   RESISTANCE IN OTHER COUNTRIES

Although rates of resistance in *Streptococcus pneumoniae* are increasing in the UK, they are lower than in many other countries. This should not encourage complacency: resistance rates comparable to current UK levels applied in France between 1984 and 1987, but thereafter penicillin resistance increased to 20% by 1992. Such swift increases often indicate clonal spread, as illustrated by events in Iceland: until l988 the rate of penicillin resistance was <1% in Iceland, but it rose to 20% by l993, reflecting import of resistant strains from Spain by returning holiday-makers, and their dissemination in child-care facilities [62]. Similar dissemination has since occurred in the USA.

| FIGURE 10 | RESISTANCE TO PENICILLIN IN *STREPTOCOCCUS PNEUMONIAE*: SEVERAL EUROPEAN COUNTRIES |

COUNTRY	YEAR(S)	RESISTANCE %
Italy	1993	0.8
Belgium	1983–88	1.5
Finland	1988–90	1.9
Germany	1979–80	6.8
Iceland	1991	9.6
Romania	1991	25.0
Spain	1989	44.3
Hungary	1988–89	57.8

Data source: reference [61].

| 10.4 | HOSPITAL-ACQUIRED GRAM-NEGATIVE RODS |

Many gram-negative rods act as opportunist pathogens in hospitals, especially for immunocompromised patients in whom virtually any site may be infected. In addition, *Escherichia coli* is the commonest cause of urinary tract infection (UTI) in the community

Rates of resistance vary according to the species: *Escherichia coli* and *Proteus mirabilis* are among the least resistant, whereas *Enterobacter* spp, *Klebsiella* spp and *Pseudomonas aeruginosa* show greater inherent or acquired resistance. Some *Acinetobacter* spp and *Stenotrophomonas maltophilia* are now resistant to all antibacterial agents, but are low-grade pathogens.

10.4.1   BASIS OF RESISTANCE

Many resistances in gram-negative rods are plasmid-mediated and transferable. This is true of most resistance to penicillins, trimethoprim, tetracycline, chloramphenicol and aminoglycosides and, increasingly, cephalosporins. In other cases, resistance

arises by chromosomal mutation: examples include most resistance to quinolones (eg ciprofloxacin), to cephalosporins in *Enterobacter* and *Citrobacter* spp, and to carbapenems in *Pseudomonas aeruginosa*. Mutations can also affect plasmid-borne genes, the major example being the evolution of 'extended-spectrum ß-lactamases'. These are mutants of classical 'TEM' ß-lactamases, whose spread has already been outlined (Section 5.2) but, unlike this parent enzyme, the mutants confer resistance to modern cephalosporins as well as to older penicillins [7].

10.4.2 RESISTANCE IN THE UK

Rates of resistance to commonly used anti-gram-negative antimicrobials are summarised in Table 10 , which shows data for isolates from blood and CSF specimens in England and Wales between l989 and l997, as reported to the PHLS Communicable Disease Surveillance Centre. Except for ampicillin and trimethoprim, most of the agents retained good activity against the major species. Retention of activity by gentamicin, which has been available since l963, is especially striking.

However, detailed examination reveals several disturbing features:

i)   In several species there is a trend towards increasing resistance, especially to cephalosporins and trimethoprim, but now also – in *Escherichia coli* – to ciprofloxacin.
ii) At introduction, ceftazidime and ciprofloxacin were active against >99% of *Escherichia coli*, *Klebsiella* and *Enterobacter* spp, not the 70–95% seen now.
iii) The favourable overall picture disguises the problems of those units where multi-resistant organisms are frequent – as in many intensive care units (see below).

10.4.3 RESISTANCE IN OTHER COUNTRIES

The rates of resistance in gram-negative rods in the UK are low by international standards. Rates are even lower in the Scandinavian countries and the Netherlands, similar to the UK in Germany, Austria and Switzerland, but higher in Southern Europe, much of Asia and the Americas. The highest rates are often in the more prosperous developing countries, eg SE Asia, Turkey and Argentina. Rates of resistance among gram-negative rods in the USAare summarised in Table 11 for comparison with Table 10, which shows UK data. The low rates of gentamicin resistance in the UK have been remarked already; they are two to three-fold lower than those for the USA in the same period. Also, rates of resistance to ciprofloxacin and ceftazidime among the UK isolates mostly compare favourably with those in the USA, which, themselves, are below those in countries where use of antimicrobial agents is unrestricted. At one extreme, it is common to see 20–40% resistance to gentamicin in gram-negative rods isolated from patients in tertiary hospitals in Southern Europe, Japan and the Americas. A l992 survey found that 70% of the *Enterobacter* isolates from Athens hospitals were resistant to cefotaxime and ceftazidime [64], and up to 60% of *Escherichia coli* are resistant to ciprofloxacin in India. Greece has long had a reputation for high rates of resistance. In the case of India, multiple 'pirated' brands of ciprofloxacin are available over-the-counter, some of low potency and all (owing to cost) prone to be under-dosed.

Higher overseas rates of resistance are a concern: they show what *can* happen. Moreover, patients infected abroad are returned or referred to the UK.

TABLE 10

RESISTANCE (%) TO ANTIBACTERIAL AGENTS IN GRAM-NEGATIVE BACTERIA FROM BLOOD AND CSF: ENGLAND AND WALES, 1989–97

ORGANISM	AGENT	1989	1990	1991	1992	1993	1994	1995	1996	1997
E. coli	Ampicillin	55	55	54	53	54	55	56	57	59
	Cefuroxime	7.2	6.3	6.8	6.1	8.6	7.1	7.1	6.9	6.1
	Ceftazidime	1.2	1.0	0.9	1.3	1.3	1.2	1.4	1.0	1.2
	Ciprofloxacin	0.5	0.8	0.7	0.9	1.2	1.7	2.0	2.6	
	Trimethoprim	19	19	19	22	24	24	28	27	29
Klebsiella spp	Gentamicin	4.1	2.7	2.5	3.0	3.3	3.7	3.0	2.9	4.2
	Cefuroxime	12	12	13	11	13	14	12	14	16
	Ceftazidime	2.7	4.2	3.6	5.2	4.4	5.7	5.5	5.7	8.0
	Ciprofloxacin	2.9	3.8	4.4	4.8	5.9	6.5	6.1	6.4	8.6
	Trimethoprim	21	24	21	22	29	27	25	25	33
Enterobacter spp	Gentamicin	3.0	2.6	2.4	2.7	3.5	3.5	3.4	4.4	4.1
	Cefuroxime	37	46	43	43	46	49	48	49	46
	Ceftazidime	19	22	22	23	25	27	26	31	28
	Ciprofloxacin	1.9	2.2	4.1	4.7	4.9	7.1	9.1	10	9.9
	Trimethoprim	18	19	20	24	25	22	28	28	30
P. aeruginosa	Gentamicin	8.1	7.3	7.3	5.4	5.0	6.1	5.5	7.9	6.8
	Azlocillin	8.2	5.2	8.6	5.2	9.4	5.9	9.7	11.4	13
	Ceftazidime	5.0	4.7	4.9	3.7	6.7	5.3	5.7	6.2	5.7
	Ciprofloxacin	4.7	6.5	6.8	6.7	8.6	7.3	9.1	9.3	11

Data source: reference [65].

TABLE 11

RESISTANCE (%) TO ANTIBACTERIAL AGENTS IN GRAM-NEGATIVE BACTERIA: USA, 1989–94

ORGANISM	AGENT	1989	1990	1991	1992	1993	1994
E. coli	Gentamicin	2.3	2.9	3.8	3.2	3.4	3.5
	Ampicillin	28	31	32	33	36	38
	Ceftazidime	1.3	0.9	1.6	1.5	1.3	1.6
	Ciprofloxacin	0.3	0.2	0.2	0.6	1.1	1.4
Klebsiella spp	Gentamicin	5.6	7.7	12	8.1	12	13
	Ceftazidime	12	11	12	11	12	13
	Ciprofloxacin	1.0	2.3	8.4	6.6	8.6	6.4
Enterobacter spp.	Gentamicin	7.1	9.4	9.4	7.2	6.2	6.0
	Ceftazidime	35	39	38	39	36	36
	Ciprofloxacin	2.8	2.1	3.1	3.8	4.5	4.4
P. aeruginosa	Gentamicin	15	14	16	13	9.5	9.7
	Ceftazidime	11	9.8	8.7	7.9	8.7	7.8
	Ciprofloxacin	4.4	3.6	4.8	6.2	7.6	10

10.5 ENTERIC PATHOGENS

Several bacterial genera are important in food poisoning. Most of these infections are zoonotic, with resistance acquired in the food animal before transmission to man via the food chain. At present, multiple drug resistance is not a significant problem in *Yersinia*, *Listeria* and Verocytotoxin-producing *Escherichia coli* O157; but it is a major problem in *Salmonella*, particularly *Salmonella typhimurium*. Resistance to quinolones

is emerging in *Campylobacter* spp. This section therefore concentrates upon salmonellae and *Campylobacter* spp.

10.5.1   SALMONELLAE

Salmonellosis is caused by over 2200 different *Salmonella* serotypes, classified according to their adaptation to human and animal hosts. Group 1 species (eg *Salmonella typhi, Salmonella paratyphi)* cause enteric fever only in humans and higher primates; group 2 species cause disease in specific animals, eg *Salmonella dublin* in cattle, *Salmonella cholerae-suis* in pigs, but only infrequently in humans; group 3 comprises the remaining 2000+ serotypes, that cause enteritis in man. The latter infections are often mild and self-limiting, but can be severe in the young, the elderly and those with underlying disease. Group 3 includes *Salmonella enteritidis*, *Salmonella typhimurium*, *Salmonella virchow* and *Salmonella hadar*, the four most important zoonotic serotypes in England and Wales.

TABLE 12

RESISTANCE (%) TO ANTIMICROBIAL AGENTS IN SALMONELLAE: ENGLAND AND WALES, 1994 AND 1996

ANTIMICROBIAL AGENTS	*S. ENTERITIDIS*		*S. TYPHIMURIUM*		*S.VIRCHOW*		*S. HADAR*	
	1994 n= 17701	1996 n= 18968	1994 n= 5603	1996 n= 5849	1994 n= 2797	1996 n= 1260	1994 n= 753	1996 n= 633
Ampicillin	5	5	59	80	11	26	31	59
Chloramphenicol	<1	<1	54	75	4	7	<1	<1
Gentamicin	<1	<1	1	1	1	<1	<1	<1
Kanamycin	<1	<1	2	3	2	16	7	4
Streptomycin	1	1	62	81	7	7	85	84
Sulphonamides	2	1	71	86	27	25	12	10
Tetracyclines	2	2	72	86	9	16	81	83
Trimethoprim	<1	<1	18	32	27	26	7	8
Furazolidone	1	<1	3	2	52	48	<1	<1
Ciprofloxacin	0.4	0.8	1	12	5	10	40	60

n = number of isolates tested.   Data source: PHLS

Most resistance is concentrated in *Salmonella typhimurium* (Table 12), and, since the l960s there has been a series of epidemics of this serotype (caused by different phage types), with increasing resistance. From 1964 to 1968 there was an extensive epidemic of multi-resistant *Salmonella typhimurium* DT 29 in bovines and humans in the UK. As a result of this epidemic and of wider concern, the Swann Committee recommended that certain antibacterial agents should be available only on prescription for veterinary use and should not be used for growth promotion [66] (Section 12.12). Legislation followed and by 1970 type DT 29 was rare in bovines. For the next 6 years only about 8% of salmonellae from cattle and 3% from humans were multi-resistant [67]. However, from 1975 to the mid-1980s there was a substantial upsurge in the incidence of multi-resistant *Salmonella typhimurium* from food animals, particularly bovines, and an increase in multi-resistant isolates from humans. Phage types DT 204, 193 and 204c predominated [68]. A feature of this period was sequential acquisition of plasmids and transposons coding for resistance to multiple antibacterial agents. This followed the introduction and use (as therapeutic agents, not growth promoters), in calf husbandry, of new antibacterial agents – notably apramycin, a gentamicin analogue [69,70]. By the end of 1990, 60% of *Salmonella* isolates from cattle were multi-resistant [71].

From 1991 to 1994 there was a further substantial increase in resistance. An important factor was epidemic spread of multi-resistant *Salmonella typhimurium* DT 104 in bovines, and its increasing isolation from man (Figure 11). Also of note, in 1994, was a significant increase in multiple drug resistance in the poultry-associated serotypes *Salmonella virchow* and *Salmonella hadar*, with many of these resistant also to ciprofloxacin.

By 1996 the four major serotypes from human cases of salmonellosis were *Salmonella enteritidis, Salmonella typhimurium, Salmonella virchow* and *Salmonella hadar*. Collectively, these comprise 89% of non-typhoid salmonellae referred to the PHLS. For *Salmonella enteritidis* – the commonest serotype – there is a low and unchanging incidence of drug resistance, mostly from individuals with recent foreign travel to Greece, Spain and Turkey [72]. However, for *Salmonella typhimurium*, 80% of isolates received in 1996 were multi-resistant and most were phage type DT 104. This strain is now established in poultry, sheep and pigs, and has been isolated from many human foods. It is increasingly resistant to sulphonamides, trimethoprim and ciprofloxacin [73]. In *Salmonella virchow,* multiple resistance is concentrated in phage types 47 and 31, mostly from patients with recent foreign travel. Because of the organism's invasive potential in man [74], resistance in *Salmonella virchow* is of therapeutic importance.

FIGURE 11   **RESISTANCE TO ANTIBACTERIAL AGENTS OF *SALMONELLA TYPHIMURIUM* DT 104 ISOLATED FROM MAN: ENGLAND AND WALES, 1982–96**
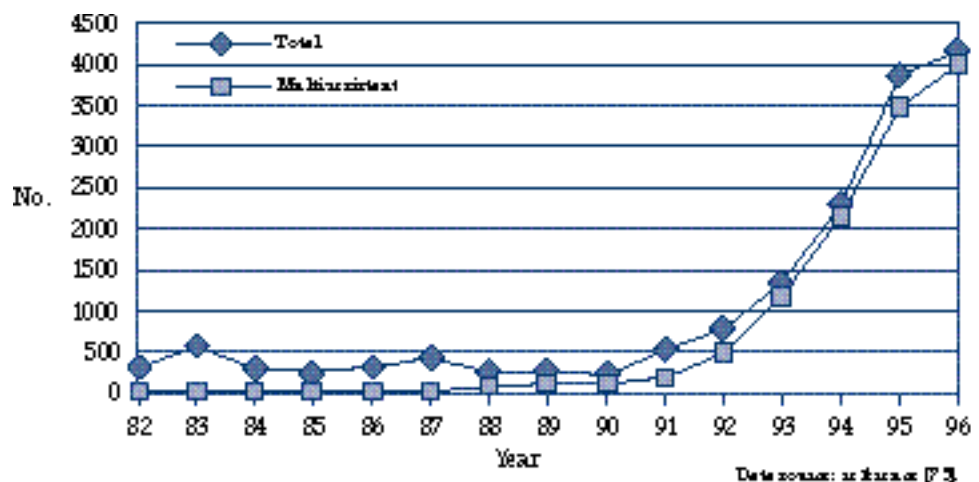
10.5.2   *CAMPYLOBACTER* SPP

Campylobacter coli and *Campylobacter jejuni* cause severe food poisoning, which may warrant antibiotic treatment. Macrolides and ciprofloxacin are used, and emerging resistance is a concern. Until recently, resistance was mostly in isolates from patients infected abroad [76]. However, the incidence of ciprofloxacin-resistant campylobacters in Oxfordshire rose from 3% in 1991 to 7% in 1995. Half of the patients gave no history of recent foreign travel. As quinolones were rarely prescribed by local GPs, it was proposed that increasing quinolone use in poultry was a likely selective factor [77]. Ciprofloxacin-resistant *Campylobacter jejuni* isolates were recovered from retail carcases of UK-bred and, especially, imported chickens [76]. Between 1982 and 1989 the incidence of ciprofloxacin-resistant *Campylobacter* spp isolated from chickens in the Netherlands rose from 0% to 14%, and this was paralleled by an increase in man from 0% to 11% . This increase followed the extensive use of enrofloxacin, a ciprofloxacin analogue, by the poultry industry [78].

In 1997, 5802 isolates of *Campylobacter* spp from humans in England and Wales were tested for drug resistance by the PHLS (Table 13). All were resistant to trimethoprim and 89% were resistant to one or more further drug. There were noticeable differences between the two main species in resistance to colomycin and tetracyclines, but both species showed disturbing (12–19%) rates of resistance to ciprofloxacin.

| TABLE 13 | RESISTANCE TO ANTIBACTERIAL AGENTS IN *CAMPYLOBACTER* SPP ISOLATED FROM MAN: ENGLAND AND WALES, 1997 |

	% RESISTANT		
ANTIBACTERIAL AGENT	*C. jejuni* (n=5401)	*C. coli* (n=376)	*C. lari* (n=25)
Ampicillin	34	46	36
Chloramphenicol	6	2	0
Erythromycin	1	13	0
Gentamicin	0.1	0.5	0
Kanamycin	1	5	60
Neomycin	1	3	4
Tetracyclines	30	27	12
Nalidixic acid	15	27	100
Ciprofloxacin	11	22	100
% resistant to one agent	50	56	100
% resistant to four or more agents	11	20	64

Data source: PHLS data.

10.5.3 OTHER ENTERIC PATHOGENS

Drug resistance, except to ampicillin, is rare in *Yersinia enterocolitica*. Intrinsic resistance to the cephalosporins, nalidixic acid and polymyxin is general in *Listeria* spp, and high-level ciprofloxacin resistance has been found in a few UK strains from humans and from food. Multiple drug resistance in *Escherichia coli* O157 is very rare, whether these isolates are from humans, human food or food animals; however, there has been an increase in resistance to streptomycin, sulphonamides and tetracyclines.

10.6   *NEISSERIA GONORRHOEAE*

Gonococci show great heterogeneity and a remarkable ability to acquire DNA from other gonococci and related species [79]. This permits rapid evolution of resistance. Sulphonamides were invariably effective against gonorrhoea on introduction in 1937 [80], but were almost invariably ineffective by 1944 [81].

Development of penicillin resistance was slower but progressive and led to the prescription of ever-increasing doses of penicillins, so that the maximum possible single dose of amoxycillin (3.5 g) is now administered to patients with gonorrhoea in the UK, together with an excretion-blocking agent (probenecid). This reduction in penicillin susceptibility reflected target modification, efflux and impermeability, and has allowed penicillin MICs to rise to 2 mg/l, giving marginal clinical resistance. It is associated with moderate cross-resistance to unrelated antibiotics, especially tetracycline and erythromycin. In the developing world, such resistance is frequently seen in all strains without plasmid-borne resistances.

Plasmid-mediated ability to produce ß-lactamases (penicillin-degrading enzymes that give high-level resistance) was first detected in 1974 in gonococci from the Far East [82] and from West Africa [83]. The origin of these 'PPNG' (penicillinase-producing *Neisseria gonorrhoeae*) is obscure, but they probably evolved in the Philippines in the early 1970s in an environment of uncontrolled and heavy ampicillin usage. PPNG soon spread world-wide. Initially the plasmids were restricted to a few phenotypes, but they disseminated gradually, with their incidence in the developing world rising to c. 50% of *Neisseria gonorrhoeae.* Spread in the UK and the Western Hemisphere was slower, and deployment of alternative antibiotics has enabled the rise to be contained and reversed. Numbers of PPNG in the UK peaked in 1983 and have since fallen, with fewer than 200 recorded in 1993.

Neisseria gonorrhoeae with plasmid-mediated tetracycline resistance were first reported in 1987 [84]; they remain uncommon in the UK but isolates from travellers indicate high prevalence elsewhere.

Ciprofloxacin is very effective against penicillin-resistant isolate, and is now used for this purpose in the UK. However, it too is used elsewhere and this is resulting in a gradual increase in MICs for UK isolates, and in a slow increase in the proportion of frankly resistant strains.

10.6.1 RESISTANCE IN THE UK

Trends in antimicrobial resistance in the UK since 1988 have been analysed by the PHLS Gonococcal Reference Unit (GRU). For specimen data the resistance patterns of all *Neisseria gonorrhoeae* isolated in Avon were assessed. These show the whole picture for a defined area with urban and rural populations. There is little resistance, but there has been a steady diminution in the proportion of strains highly sensitive to penicillin (Table 14). There is also a worrying arrival of small, but increasing, numbers of ciprofloxacin-resistant gonococci (Table 15) .

More generally, data for isolates referred to the GRU from England and Wales suggest that resistance is rising very slowly, perhaps via the success of imported strains and the selection of less sensitive strains by the inadequate dosing necessitated by single-shot treatments (Section 12.5). The availability of alternative antibacterial agents, such as ciprofloxacin, has enabled containment of the problem. In the developing world the situation is far worse, with very high levels of resistance engendered by lack of alternative antibacterial agents and misuse of available drugs. At the other extreme, resistance (and gonorrhoea) have been contained in Sweden, where most cases are now imported [85].

TABLE 14

RESISTANCE TO PENICILLIN IN *NEISSERIAGONORRHOEAE* ISOLATES: COUNTY OF AVON, 1988–96

RESISTANCE CATEGORY (MIC range, mg/l)	PENICILLIN* PHENOTYPE	NUMBER OF ISOLATES (% of total)								
		1988	1989	1990	1991	1992	1993	1994	1995	1996
Sensitive (<0.1)	–	281 (55)	214 (38)	274 (43)	183 (32)	70 (16)	114 (36)	59 (18)	50 (17)	31 (11)
Intermediate (0.1 – 1)	–	202 (40)	335 (60)	339 (53)	370 (65)	363 (81)	191 (61)	256 (76)	201 (68)	227 (77)
Resistant (>1)	+	11 (2.2)	6 (1.1)	15 (2.4)	14 (2.4)	11 (2.5)	3 (1.0)	13 (3.9)	38 (13)	22 (7.5)
	–	13 (2.6)	4 (0.7)	8 (1.3)	6 (1.0)	2 (0.5)	7 (2.2)	7 (2.1)	8 (2.7)	15 (5.1)
Total		507	559	636	573	446	315	335	297	295

* + = PPNG. Data source: PHLS Gonococcal Reference Unit.

TABLE 15

SUSCEPTIBILITY TO CIPROFLOXACIN OF ALL *NEISSERIAGONORRHOEAE* ISOLATED IN THE COUNTY OF AVON 1988–96

RESISTANCE CATEGORY (MIC range, mg/l)	PENICILLIN* PHENOTYPE	NUMBER OF ISOLATES (% of total)								
		1988	1989	1990	1991	1992	1993	1994	1995	1996
		507	559	637	573	444	322	334	294	287
Sensitive (<0.05)	–	98.8	98.9	97.6	97.6	97	89	95.8	86.9	91.5
	+	1.2	1.1	2.4	2.4	2.5	12.1	3.9	12.1	5.8
						2	3		2	4
Intermediate (0.05–0.9)	–					0.5	1.0		0.3	0.3
	+								0.3	1.0
								1	1	4
Resistant (≥1)	–							0.3		0.7
	+								0.3	0.7

* + = PPNG. Data source: PHLS Gonococcal Reference Unit.

NEISSERIA MENINGITIDIS

Neisseria meningitidis is the major cause of bacterial meningitis. It is related to *Neisseria gonorrhoeae,* but is less adept at acquiring resistance. This is fortunate, considering the greater severity of the disease and the difficulty of drug delivery to the site of infection. The PHLS Meningococcal Reference Unit (MRU) performs susceptibility tests with a limited range of antibacterial agents, aiming to provide epidemiological information rather than to inform individual patient management, which has invariably been initiated by the submitting institution. The antibacterial agents tested are benzylpenicillin, which is the mainstay of therapy; rifampicin and ciprofloxacin, which are currently used for carriage eradication ('chemoprophylaxis') in close contacts of disease cases; and sulphonamides, which previously were used for chemoprophylaxis.

10.7.1   RESISTANCE IN THE UK

Neisseria meningitidis isolates frankly resistant to benzylpenicillin have not yet been identified in England and Wales, but were reported from South Africa [86] and more

recently from Spain [87]. Isolates with reduced penicillin susceptibility occur in the UK, and monitoring is vital. Since 1984 the proportion of UK isolates with reduced penicillin susceptibility has increased from <1% in 1985/6 to nearly 14% in 1995/6. An upward trend in the mean penicillin MIC was seen until 1995/6, but reversed in 1996/7 (Figure 12). The number of isolates with an MIC of 1.28 mg/l has never exceeded three in any 1 year, and in most years there have been none.

FIGURE 12   **PROPORTION OF CLINICAL *NEISSSERIA MENINGITIDIS* ISOLATES HIGHLY SENSITIVE TO PENICILLIN (MIC <0.1 mg/l)**
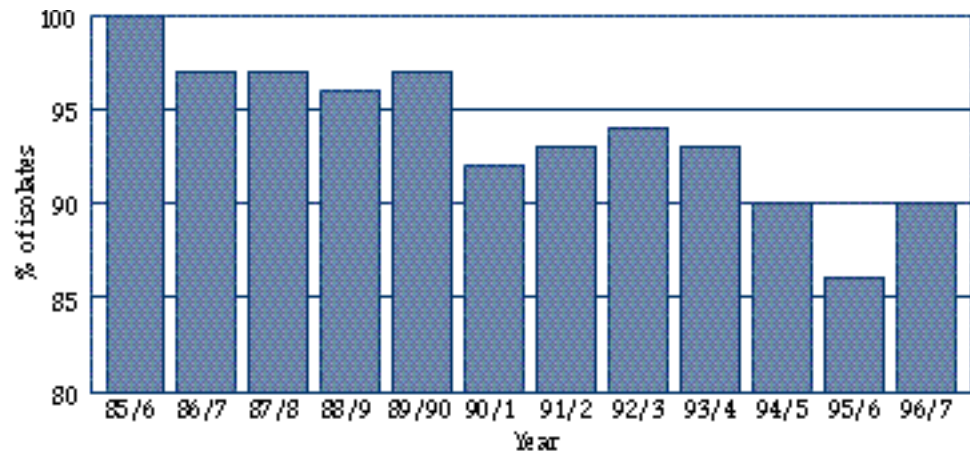
Data source: PHLS Submission to House of Lords enquiry.

Rifampicin is the most widely used prophylactic agent for contacts of meningococcal cases. Resistance is defined as an MIC >5 mg/l, and the proportion of resistant isolates has never exceeded 0.4% in any given year. Most of the resistant isolates are from those who have received recent rifampicin chemoprophylaxis, an observation that accords with the ability of rifampicin to select mutational resistance and highlights the need to use chemoprophylaxis in a targeted fashion, and sparingly. In age groups where ciprofloxacin can be safely prescribed, it is increasingly used for chemoprophylaxis. Ciprofloxacin MICs have been monitored since 1993; all isolates examined to date have been very susceptible (MIC <0.1 mg/l). Sulphonamides were previously used for chemoprophylaxis, but resistance (MIC >10 mg/l) became a major problem, reaching 40% in the mid-1980s.

10.8   *MYCOBACTERIUM TUBERCULOSIS*

Tuberculosis (TB) remains the commonest bacterial cause of death from any single infectious agent in adults world-wide, with an estimated 8 million new cases and 3 million deaths annually, mostly in the developing world. A steady decline in clinical cases in the developed world, and some parts of the developing world, ceased or reversed in the mid-l980s. There have been several contributing factors:

1) Co-infection with the human immunodeficiency virus (HIV)
2) Failure to give priority to national TB control programmes
3) Reduction or withdrawal of donor agency support to international TB control programmes
4) Increasing numbers of homeless or displaced persons sheltering in overcrowded conditions
5) Intravenous drug use
6) Immunocompromise, due to extremes of age, alcoholism, diabetes mellitus, renal failure
7) Increased immigration from countries of higher prevalence.

Unusually among bacterial infections, *Mycobacterium tuberculosis* infections require treatment with combinations of three or four agents for at least 6 months. Monotherapy leads rapidly to resistance, by selecting spontaneous mutants. Even with combination therapy, resistance emerges when there is non-compliance by the patient, incorrect dosage by the physician or malabsorption.

The greatest treatment problem relates to individuals with multi-resistant TB isolates – defined as those resistant to both isoniazid and rifampicin, with or without other resistances. Mortality is high and reached 44% in a landmark study in HIV-negative patients, despite individualised treatment. The mortality rate in HIV-positive patients can be as high as 80–90%. Recent studies in New York have demonstrated significantly improved outcomes when more than two drugs retained activity against an isolate. Rapid detection of resistance is vital for the individual, and for public health, as patients can then be rendered non-infectious earlier than otherwise.

10.8.1   RESISTANCE IN ENGLAND AND WALES

A review was carried out of *Mycobacterium tuberculosis* isolates submitted to the PHLS from residents of England and Wales between 1982 and 1991 [88]. Overall, 6.1% of 'initial isolates' (ie first isolates from newly diagnosed patients) were resistant to isoniazid and 0.6% were multi-drug resistant. No increasing trend was observed, but in view of the international emergence of resistance, the PHLS, together with colleagues in Scotland and Northern Ireland, established a surveillance system 'MYCOBNET', collecting prospective data for the whole of the UK. Isoniazid resistance rates (with or without resistance to other drugs) were 4.6%, 5.4% and 5.5% in l993, l994 and l995 respectively. Multi-drug resistance rose from 0.6% in l993 to 1.2% in l994 and l995.

10.8.2   RESISTANCE IN OTHER COUNTRIES

Resistance rates in *Mycobacterium tuberculosis* are higher in the USA, where a 1993–96 survey estimated that 8.4% of isolates were initially resistant to isoniazid and 2.2% were multi-drug resistant [89]. Compared with previous US surveys in l991 and 1992, isoniazid resistance had remained relatively stable and multi-drug resistance had decreased a little. In some parts of the developing world multi-drug resistance is especially frequent.

10.9   FUNGAL INFECTIONS

Fungal infections are assuming greater importance, largely because of their increasing incidence in patients with AIDS, transplant recipients, neutropenic cancer patients and debilitated intensive care patients. In the 1980s there was an 11-fold rise in the incidence of disseminated candidosis among patients admitted to hospitals in the USA [90]. In the same period, *Candida* spp became the fourth most common cause of nosocomial bloodstream infections in US hospitals, accounting for 8–10% of all hospital-acquired bloodstream infections [91]. In the Netherlands, the rate of bloodstream infections caused by *Candida* spp doubled between 1987 and 1995 [92]. There are no comparable data for the UK.

10.9.1   RESISTANCE TO ANTIFUNGAL AGENTS

The unwelcome rise in the number of serious fungal infections has resulted in a marked increase in the use of antifungal agents. This has contributed to the emergence of resistance to a number of important compounds, although the clinical impact of this problem has differed from one group of patients to another. Drug resistance has been identified as a major cause of treatment failure among patients treated with flucytosine [93]. However, use of this compound has been declining. Until the 1990s, acquisition of resistance to azole antifungal agents (which are the most important group of ergosterol biosynthesis inhibitors) was exceptional [93]. In recent years, however, resistance to these agents has become a significant problem in several groups of patients, notably those with AIDS [3].

Oral candidosis is often the earliest infectious complication encountered in HIV-infected individuals [94] and occurs in 80–90% of patients with AIDS, becoming more prevalent and less responsive to treatment as the immunological defence mechanisms of the host become more impaired. These infections are mostly caused by *Candida albicans.*

Fluconazole, introduced in the late 1980s, proved an excellent agent for the treatment of mucosal candidosis. Fluconazole is well-tolerated and safe and these factors led to a rapid expansion in its use – at low dosages and for long periods – to prevent relapse in patients with HIV-related mucosal candidosis. In 1992, the first reports appeared, from Madrid and Paris, of failures of fluconazole treatment in significant numbers of AIDS patients with oral or oesophageal candidosis. Since then, resistant strains of *Candida albicans* have been reported world-wide [3]. The recent introduction of the antiretroviral protease inhibitors has led to a reduction in the number of new cases of azole drug resistance in fungi from AIDS patients, but it remains to be seen whether this improvement can be sustained.

The impact of fluconazole on the management of other groups of immunocompromised and debilitated patients has also been considerable. In addition to treatment of intensive care and surgical patients, this agent has been used on a large scale for prophylaxis in neutropenic cancer patients and following bone marrow transplantation (BMT). It has been possible to document a shift from azole-susceptible organisms, such as *Candida albicans*, to intrinsically fluconazole-resistant species such as *Candida glabrata* and *Candida krusei*. This shift has been best documented among BMT recipients exposed to fluconazole prophylaxis [95], but has also occurred in other hospital populations. In one report from the USA, the proportion of blood culture isolates identified as *Candida albicans* fell from 89% to 30% in the period from 1987 to 1992, while the proportion of isolates identified as *Candida glabrata*, *Candida parapsilosis* or *Candida tropicalis* increased [96]. This shift in species distribution is not solely related to increased fluconazole use, but it may be an important factor. Up to 50% of *Candida tropicalis* isolates are resistant to fluconazole [97] and many are cross-resistant to other azoles [98].

Vaginal candidosis is one of the commonest infections seen in general practice in the UK. Up to 75% of all women will suffer at least one episode of this condition, and many have recurrent disease. *Candida albicans* accounts for 80–95% of these infections, but 5–10% of cases are due to *Candida glabrata*. In marked contrast to *Candida albicans*, isolates of *Candida glabrata* become resistant to azole antifungal agents after short periods of exposure [99]. Once azole treatment has failed to control vaginal infection with *Candida glabrata*, management of the condition becomes much more difficult and chronic or recurrent disease is common [100].

TABLE 16

ANTIFUNGAL AGENTS AVAILABLE IN THE UK

ANTIFUNGAL DRUGS	INTRODUCED	RESISTANCE CONCERNS
Polyenes		
Nystatin	1953	Much used in treatment of superficial candida infections.
Amphotericin B	1956	Remains the 'gold standard' for most systemic fungal infections.
		Occasional reports of resistance following prolonged use in immunosuppressed hosts.
Griseofulvin	1958	Long the drug of choice for dermatophytosis. Now being replaced by azoles and allylamines. Resistance is rare.
Flucytosine	1964	Narrow-spectrum drug used in combination with amphotericin B or triazoles for candidosis or cryptococcosis. Frequent reports of resistance.
Imidazoles		
eg Clotrimazole	1972	Large group of compounds used for topical treatment of cutaneous and mucosal infections.
Miconazole		
Ketoconazole	1978	Useful oral agent. Resistance reported following prolonged use in immunosuppressed patients.
Triazoles		
Itraconazole	1984	Important agents for oral treatment of systemic fungal infections. Resistance becoming more common especially in immunosuppressed patients. Many isolates cross-resistant to all azole agents.
Fluconazole	1985	
Allylamines		
Terbinafine	1984	Now the drug of choice for most forms of dermatophytosis. Resistance is rare.

10.10   VIRAL INFECTIONS

10.10.1   EVOLUTION OF ANTIVIRAL RESISTANCE

Over 20 antiviral drugs are now available in the UK and the major compounds are listed in Table 17. Targets include herpes viruses, HIV, influenza and hepatitis B, and will soon extend to hepatitis C and papillomaviruses. Resistance to virtually all the compounds has been documented. Where suitable propagation systems exist, resistant viruses can be generated by *in-vitro* passage with increasing drug concentrations. Thus, knowledge of resistance often pre-dates licensing. Resistance generally accrues step-wise by mutation, and often leads to a virus with reduced susceptibility rather than one with frank clinical resistance.

Resistance to antiviral agents has so far commanded far less concern than that to antibacterial agents. This reflects three key differences:

i) Effective antiviral agents are a more recent development than antibacterial agents.
ii) Detection of resistance is harder than with antibacterial agents, as viruses may be more difficult to propagate on synthetic media.
iii) Because of the difficulty in testing for resistance, there are very few good epidemiological studies.

Clinically, three key factors affect the likelihood (or not) of emergence of resistance, and their importance varies with the combination of virus and drug.

a) **Mutation rate** Resistance is caused by single or multiple mutations. As with bacteria, mutants exist within the individual's viral population prior to therapy but a drug's selective pressure encourages their expansion to become the majority population. RNA viruses (eg HIV), do not 'proof-read' genes during replication and so generate resistant mutants more rapidly than DNA viruses (eg the herpes family) which do proof-read. In addition, the risk of resistant mutants emerging depends on the total number of virus particles and on their replication rate. Chronic infections with rapid turnover, eg HIV, HCV and HBV are ideally suited to the development of resistance. Reduced immune function increases the viral load and replication rate, also increasing the risk of resistance.

b) **Viral 'fitness'** Viruses are exquisitely adapted to their hosts. Drug-selected mutants may initially have reduced fitness but, as with bacteria (see Section 13.2) there are now many examples of 'compensatory' mutations that allow these resistant mutants to regain their fitness.

c) **Drug potency** If a drug completely stops viral replication, resistance should not appear. In contrast, a drug with minimal potency will not exert sufficient selective pressure to generate resistance. The ideal circumstances in which resistance will occur arise where potent antiviral agents are used suboptimally, eg as monotherapy or dual therapy for HIV, or where there is poor drug compliance.

TABLE 17	ANTIVIRAL AGENTS LICENSED OR AVAILABLE FOR COMPASSIONATE USE IN THE UK (JUNE 1998)

DRUG	TARGET VIRUSES
Amantadine, rimantadine	Influenza A treatment and prophylaxis
Ribavirin	Respiratory syncytial virus (RSV), Lassa fever, (trials in hepatitis C)
Idoxuridine	Topical therapy of herpes simplex keratoconjunctivitis
Famciclovir	HSV, VZV (trials in hepatitis B)
Aciclovir	HSV, VZV
Valaciclovir	HSV, VZV
Ganciclovir	CMV
Zidovudine (ZDU), formerly called azidothymidine (AZT)	HIV
Foscarnet (phosphonoformic acid)	HSV, VZV, CMV
Cidofovir	CMV
Lamivudine (3TC)	HIV (trials in HBV)
Zulcidabine, didanosine, stavudine, nevirapine, delavirdine, efavirenz, saquinavir, indinavir, ritonavir	HIV

10.10.2   RESISTANCE IN CLINICALLY IMPORTANT VIRUSES

10.10.2.1   Herpes viruses

Herpes infections include cold sores (caused by herpes simplex virus 1, HSV1), genital herpes (mostly HSV2), chickenpox and shingles (varicella zoster virus, VZV). In healthy individuals these infections are self-limiting, but therapy may be used to shorten or alleviate symptoms. These same viruses and also cytomegalovirus (CMV) cause severe disease in immunocompromised individuals, in whom resistance is increasingly common, reflecting a faster viral replication rate and prolonged periods of aggressive therapy.

10.10.2.2 Herpes simplex virus (HSV)

Aciclovir-resistant HSV is particularly problematic in AIDS patients and BMT recipients. The HSV Task Force [101] estimated that 4% of isolates from AIDS patients have reduced drug susceptibility. A similar rate of resistance was seen in isolates from BMT patients receiving aciclovir [102]. Foscarnet remains the second-line therapy of choice [103]. Alternative drugs include **topical** preparations of cidofovir, trifluorothymidine and foscarnet but none of these is yet licensed in the UK. Selection of resistance in non-immunosuppressed patients (eg during therapy for recurrent cold sores or genital herpes) appears very uncommon in practice [101], as resistant virus is generated at the epithelial surface whereas recurrence reflects reactivation of (still sensitive) virus from the dorsal root ganglion.

10.10.2.3 Varicella-Zoster (VZV) and cytomegalovirus

VZV: Reactivation of aciclovir-resistant VZV in the immunocompromised patient can be devastating, but is rare compared with drug-resistant HSV. Only one case of visceral aciclovir-resistant VZV has been described. As with HSV, foscarnet is the second-line drug of choice [91].

Cytomegalovirus (CMV): CMV is a major cause of morbidity and mortality in transplant and AIDS patients. Whereas treatment of HSV and VZV with antiviral agents is generally successful, this cannot be said of CMV, and mortality from pneumonitis in BMT recipients remains high, despite the use of ganciclovir. Similarly, CMV retinitis in AIDS patients is progressive, and the best that can be achieved – by lifelong therapy – is a delay in progression. As the efficacy is poor, it has been difficult to associate failure with viral resistance. Nevertheless, long-term therapy (>3 months) with intravenous ganciclovir for CMV retinitis in AIDS was associated with c. 8% prevalence of resistance [105], whereas little resistance was detected in BMT patients receiving ganciclovir for 18–26 days [106]. Available data suggest that very little resistance emerges during oral ganciclovir therapy, even when this lasts for 100–120 days [105].

10.10.2.4 Hepatitis B (HBV)

Interferons have limited efficacy in HBV infection. Recent clinical trials of the nucleoside analogues lamivudine (3TC) and famciclovir have assessed efficacy in reducing HBV load and preventing re-infection after liver transplant and suggest that these drugs represent a considerable advance [107,108]. They target the HBV polymerase (POL) and clinical trials have shown that POL mutations are associated with clinical failure in man [109]. The estimated 1-year incidence of lamivudine resistance in chronic HBV patients is 14% [110].

10.10.2.5 Human immunodeficiency virus (HIV)

Anti-HIV drugs include nucleoside inhibitors of reverse transcriptase, of which the first was zidovudine (ZDV), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors. Since the first report of HIV resistance to zidovudine in 1989 [111], a huge literature has accrued, with many mutations documented as conferring resistance to different reverse transcriptase and protease inhibitors.

As a general principle, maximal suppression of the plasma HIV load limits the emergence of resistance. This observation provides the rationale of highly active antiretroviral therapy (HAART), now increasingly being used. This is based on double, treble and even quadruple therapy and may encompass all three different classes of anti-HIV drug. These combinations lead to the emergence of novel patterns of resistance, which often cannot be predicted from the monotherapy results. Thus, lamivudine monotherapy rapidly selects for a resistance mutation at position 184 of the reverse transcriptase, but this change re-sensitises zidovudine-resistant HIV to zidovudine [112], and may explain in part, the efficacy of ZDV/lamivudine in combination.

Surprisingly little evidence exists for a causal relationship between resistance and clinical failure in HIV disease. This is because of the many confounding variables, eg CD4 cell count decline, syncytium-inducing phenotype, and most importantly, plasma viral load. The most conclusive data on the clinical role of resistance was from a study that randomised zidovudine-experienced patients to (i) continued zidovudine monotherapy or (ii) didanosine monotherapy. High-level zidovudine resistance at randomisation was a risk factor for progression, regardless of the subsequent therapy [113].

10.10.2.6 Influenza

Amantidine and its analogue rimantidine are the only licensed anti-influenza treatments, and are active only against influenza A. Resistant mutants have been isolated *in vitro* and *in vivo*. They arise rapidly in up to 30% of individuals treated, although there are few data on the degree to which their emergence limits efficacy in the individual. Resistant viruses appear to be as pathogenic as sensitive ones.

It is to be anticipated that resistance will also develop to the new neuraminidase inhibitors, presently in phase III trials, which have good activity against both influenza A and B.

10.10.3   TRANSMISSION OF RESISTANT VIRUSES

The public health implications of antiviral drug resistance depend on the capacity of the mutated viruses for transmission and their capacity to cause disease. This, in turn, depends on the route and inoculum of transmission, and the 'fitness' of the variants to replicate in the absence of the drug.

10.10.3.1 Herpes viruses

As herpes virus infections in immunocompetent patients are usually self-limiting, the implications of transmission are far less severe than for HIV. Only one case of transmission of drug-resistant HSV has been documented – from an HIV-infected individual to an immunocompetent sexual partner [114]. No similar cases of CMV or VZV transmission have been reported, although this by no means excludes the possibility.

10.10.3.2 HIV

Evidence of transmission of resistant HIV is anecdotal, but important. Imrie *et al* [115] reported transmission of HIV from a zidovudine- and nevirapine-experienced gay man. Nevirapine-resistant virus was detected in the recipient soon after infection, but the zidovudine-resistant virus became detectable only after some weeks of zidovudine therapy. These data suggest that resistant virus was transmitted and rapidly became the majority population under selective pressure. A handful of reports have documented an increasing prevalence of zidovudine-resistant mutations in untreated individuals or those with primary infection.

The increased use of HAART at earlier stages of infection may increase the risk of transmission, because patients will remain 'well' for longer and, in some cases may be more likely to pass on the infection. On the other hand, suppression of viral replication by HAART should reduce the overall risk of virus transmission by reducing the viral load.

10.10.3.3 Influenza

In view of the high mutability and transmissibility of influenza, it is not surprising that phenotypically resistant isolates have been identified in drug-naive individuals. Illnesses caused by apparent transmission of resistant virus have occurred in household and nursing home contacts receiving amantidine and rimantidine prophylaxis. These data represent the most conclusive evidence for transmissibility of drug-resistant viruses in general.

10.11 WHAT NEXT FOR ANTIMICROBIAL RESISTANCE?

Experience shows that existing resistances will spread and that new types will evolve. The past decade has revealed new genetic mechanisms – mosaic gene formation [10] and integrons [116] – that facilitate the evolution and spread of bacterial antimicrobial resistance. The decade has also shown that the importance of efflux as a resistance mechanism was underestimated previously [117]. More fundamentally, evolution – from unicell to dinosaur to man – has run more swiftly than would be predicted from known genetic processes, implying the existence of processes that we do not yet understand. A controversial proposal by Cairns *et al* [118] is relevant in this context, that bacteria undergo favourable mutations under selection pressure. Such a mechanism would accelerate the evolution of resistance.

Several key developments can be predicted.

First, it seems inevitable that vancomycin-intermediate MRSA(VISA) will spread. Even during the few months that this Sub-Group has been in existence, VISA have been encountered in the USA and France, as well as in Japan, where they were first reported [48–50]. Worse, gene exchange can occur between enterococci and staphylococci, and it is likely that the VanA system of enterococci will spread to MRSA, giving high-level glycopeptide resistance. Spread of VanA to *Streptococcus pneumoniae* and other α-haemolytic streptococci is also possible, in the same way that other enterococcal and staphylococcal genes transfer to these genera [119]. Again, the consequences would be severe: glycopeptides are the drugs of last resort against ß-lactam-resistant α-haemolytic streptococci in endocarditis, and against ß-lactam-resistant *Streptococcus pneumoniae* in meningitis.

Second, gram-positive organisms pose the greatest current concern, but gram-negative bacteria susceptible to only one or two antibacterial agents are common.

Often, the last drugs to retain activity are the carbapenems – imipenem and meropenem. Carbapenem resistance is now found increasingly in *Acinetobacter* spp world-wide [120]. Furthermore, plasmid-mediated carbapenemases (carbapenem-destroying enzymes) have emerged in enterobacteria and *Pseudomonas* spp in Japan [121]. These enzymes give complete resistance to all ß-lactams. They have a flexible structure, with a large active site, implying that it will be extremely difficult to re-design ß-lactams that evade hydrolysis. During the 6 months following the establishment of the SMAC Sub-Group, the PHLS Antibiotic Reference Unit has received *Pseudomonas aeruginosa* isolates from England with a carbapenemase and with complete antimicrobial cross-resistance. These are under study, but their enzyme is not identical to that from the Japanese strains [122].

Third, quinolones have retained good activity against many gram-negative rods resistant to other antibacterial agents and, until 1997, resistance had always proved to be mutational, not plasmid-associated. However, in 1997, an *Escherichia coli* isolate was described in Spain with transferable quinolone resistance [123]. This seems likely to spread.

Other resistances to be feared include those in species that have, thus far, remained remarkably susceptible. Obvious risks are penicillin resistance in *Neisseria meningitidis* and *Streptococcus pyogenes*. Resistance in *Neisseria meningitidis* follows the same evolutionary course as in *Neisseria gonorrhoeae*, albeit more slowly, and there is every reason to suppose that substantive penicillin resistance will ultimately emerge. Penicillin resistance in *Streptococcus pyogenes* is remarkable for its continued absence: once the most feared of hospital wound pathogens, this species has remained exquisitely sensitive to penicillin since the 1940s. Nevertheless, gene exchange occurs between *Streptococcus pyogenes* and staphylococci [119], and there is a risk that ß-lactamase production may spread from the latter to the former.

In short, evolution hasn't finished yet...

11 AREAS OF CLINICAL PRACTICE WHERE ANTIMICROBIAL RESISTANCE HAS, OR IS LIKELY TO HAVE, THE GREATEST IMPACT

Resistance is most severe in environments where large numbers of susceptible patients tend to be concentrated. These are exactly the situations where antimicrobial chemotherapy is most often essential. Nevertheless, the consequences of resistance are not restricted to specialised units and are seen in general in-patients and in the community.

11.1 INTENSIVE CARE UNITS

Resistance is most common in patients receiving mechanical ventilation and in university or teaching hospitals [14]. Intensive care and similar units present special problems. Ventilator-associated pneumonia caused by antibiotic-resistant bacteria has become recognised as a particularly important problem, and often follows previous exposure to antibiotics [124]. The excess of resistance in ICU isolates is illustrated in Table 18, comparing rates among *Pseudomonas aeruginosa* isolates from ICUs, other hospital sources and in the community. Resistance rates in the ICU isolates were at least double those in the community isolates.

Heavy use of antibiotics is probably the major factor behind the high rates of antibiotic resistance in ICUs. In addition, ICU patients may be subjected to invasive support activities that increase the risk of infection, demanding more antibiotic treatment and enhancing the risk of selecting resistance. Risk factors include the use of invasive devices such as vascular and urinary catheters as well as ventilation [125,126]. Other factors include increased length of ICU stay (>48 hours), trauma and catheterisation (central venous, pulmonary artery or urinary).

The consequences are severe: ICU-acquired pneumonia, clinical sepsis and bloodstream infection all increase mortality [127].

Future efforts should be aimed at improving diagnosis, excluding infections and improving antibiotic administration in the ICU [124] or, as Cuhna eloquently puts it [128]:

'Intensive care not intensive antibiotics!'

TABLE 18

RESISTANCE (%) OF *PSEUDOMONAS AERUGINOSA* ISOLATES BY PATIENT GROUP: UK

ANTIBACTERIAL AGENT	ICU PATIENTS (n=134)	GENERAL IN-PATIENTS (n=1042)	OUT-PATIENTS (n=797)
Gentamicin	18.6**	11.3	10.8
Amikacin	15.6*	9.5	10.2
Ciprofloxacin	15.6**	8.4	6.6
Ceftazidime	20.1**	11.0	6.0**
Carbenicillin	21.6**	12.7	8.5**
Azlocillin	24.6**	13.1	5.5**
Imipenem	9.7	1.9	2.1
Meropenem	6.7	0.8	0.6

Significantly different from the isolates from general in-patients *p <0.05; ** p <0.01.
Data source: reference [129].

11.2 ADMISSIONS WARDS

A large proportion of the patients admitted to hospital as emergencies are prescribed antimicrobial agents. Over the last decade there has been a 50% increase in emergency admissions to general hospitals in the UK [130]. General hospitals increasingly accept emergency patients on an admissions ward where a pre-registration house physician – often the most junior doctor on the admitting team – makes a provisional diagnosis, orders investigations and prescribes treatment. Most of these patients have 'medical' rather than surgical problems and so are admitted under physicians. An average district general hospital might receive 25 such patients per day; a large city hospital might receive twice this number. Many of the patients are elderly; while the diagnosis in many is obvious (eg cerebrovascular accident, myocardial infarction), in others it is uncertain (eg 'dizzy, off legs').

Infections of the respiratory and urinary tracts are common in these patients. However, the bedside evidence for infection often is not obvious and diagnosis of infection relies on samples being sent to the microbiology laboratory. Meanwhile, the junior doctor has to decide whether or not to prescribe empirically.

This prescribed therapy should be reviewed at an early time by a more senior physician, ideally a consultant [131], but pressures on the admitting medical team are often intense and senior review is often delayed by hours or even days – often until the next consultant ward round.

While most hospitals have antimicrobial prescribing policies, these are often not 'user friendly' to the harassed junior doctor in the middle of the night, whose immediate superior (a middle grade doctor) may be busy elsewhere, resulting in excessive use of broad-spectrum and expensive antibiotics. This provides many opportunities for inappropriate or unnecessary antimicrobial prescribing.

It is likely that much antimicrobial prescribing on admission wards is unnecessary, inappropriate, or 'defensive'.

11.3   OTHER IN-PATIENTS

Although resistance presents the greatest risks to severely ill patients and those in specialised units, its more general threat should not be underestimated. Many surgical procedures that now seem routine, eg prosthetic joint replacement and 'dirty' gut surgery, depend on protection with antimicrobial prophylaxis. Accumulating resistance undermines these procedures, increasing morbidity, length of hospital stay and, thereby, costs.

11.4   IMMUNOCOMPROMISED PATIENTS, INCLUDING THOSE WITH HIV INFECTION

Immunocompromise is a feature of many medical conditions. It may also result from the treatment the patient has undergone. Thus immunosuppression is induced to prevent the organ rejection which may follow transplant surgery and is an unwanted side-effect in many anticancer regimens. Alternatively, immunosuppression may be a consequence of the underlying illness, for example in patients with burns there is a transient natural immunosuppression.

Those with AIDS/HIV infection represent another important group of immunosuppressed patients. The recent improvement in their life expectancy associated with advances in antiviral therapy has been accompanied by the parallel appearance of resistance to antiviral agents. This was addressed further in Section 10.10.

Immunocompromised patients may present with difficult-to-diagnose or occult infections, many caused by bacteria but some by fungi. Moreover, such patients are vulnerable to a wide range of opportunist infections and often require urgent empirical treatment, without the opportunity to take appropriate microbiological samples.

The problems associated with resistance to antifungal treatment are addressed in Section 10.9.

11.5   OUT-PATIENTS

The spread of resistance in community pathogens, especially *Streptococcus pneumoniae*, undermines antibiotic therapy outside the hospital. Clinical failures caused by resistance add to costs and to morbidity. In some instances – especially with multi-drug resistant *Streptococcus pneumoniae* – it becomes necessary to give parenteral rather than oral therapy, necessitating hospitalisation.

Tuberculosis represents a special case. Resistance here is associated with therapeutic failure and, therefore, with an increased likelihood of transmission, multiplying human suffering and cost.

| BOX 9 | **ENDOCARDITIS (INFECTION OF THE HEART VALVES)** |

Endocarditis is mostly caused by α-haemolytic streptococci, enterococci, or more rarely, coagulase-negative staphylococci. Other organisms may be involved, especially in intravenous drug users.

Effective therapy demands the use of combinations of antibacterial agents, with strong bactericidal activity (ie with the ability to kill the bacteria, not merely to inhibit their growth). Widely used combinations against streptococci and enterococci are: penicillin plus aminoglycoside or vancomycin plus aminoglycoside. Both therapies are under threat. Resistance to all the relevant agents is already common in enterococci; and in α-haemolytic streptococci, the PHLS Antibiotic Reference Unit is seeing increasing numbers of isolates with reduced penicillin susceptibility and/or high-level aminoglycoside resistance. As a result, non-conventional regimens have to be recommended with agents (eg rifampicin) that carry a significant risk of mutational resistance.

Without new therapies, it seems likely that treatment of endocarditis will be compromised sooner rather than later.

11.6   DENTAL USE OF ANTIMICROBIAL AGENTS

Dental prescribing accounts for only about 7% of total antibiotic use in primary health care. Nevertheless, dental usage is substantial in absolute terms, with dental practitioners writing 3.3 and 3.5 million prescriptions for antibiotics in 1993 and 1996, respectively. In the case of metronidazole – a drug also used against anaerobic bacteria in surgical infections – dental prescribing accounted for 40% of all metronidazole prescriptions in the community services of the NHS in 1993 and 45% in 1996.

Increased dental use of antibiotics in recent years may be related to the treatment of periodontal disease. Nevertheless, the majority of such use is for the treatment of localised oral infections and for the prophylaxis of endocarditis in high-risk patients undergoing extractions. Edlund *et al* [132] noted that a subset of juvenile and adult patients with periodontal disease benefited from antibacterial agents, and emphasised that the drug choice should be based on 'accurate microbial analysis of the sub-gingival flora and *in-vitro* susceptibility tests of the most important periodontal pathogens'. These authors favoured the use of topical agents as causing the least general disturbance of the gut microflora, but did note a risk of resistance emerging at the site of infection. This concern is reinforced by an *in-vitro* study [133] showing that several periodontal pathogens, most notably *Actinobacillus actinomycemcomitans*, could develop mutational resistance to tetracyclines (including minocycline) and metronidazole, which are active antibacterial agents in several local treatments for periodontal infection.

A controversial suggestion is that amalgam fillings may contribute to the burden of resistance by selecting for mercury resistance plasmids, which in turn may co-determine resistance to antibacterial agents [22]. Recent studies argue against this hypothesis, showing no difference in the prevalence of resistant gut bacteria between those who do and do not have amalgam fillings [134,135].

TABLE 19

ANTIBACTERIAL AGENTS PRESCRIBED BY DENTISTS AS PERCENTAGES OF ALL AGENTS DISPENSED IN THE COMMUNITY IN ENGLAND, 1993–96

ANTIBACTERIAL AGENT (BNF 5.1)	1993	1994	1995	1996
Penicillin V	17.2	15.5	13.8	13.6
Amoxycillin	9.9	11.3	10.4	11.3
Erythromycin	8.4	8.4	7.1	7.3
Metronidazole	39.7	41.5	43.3	45.0
Total antibacterial agents dispensed (BNF 5.1 – 5.3)	6.7	7.2	6.7	7.1

Data source: Statistics Division of the Department of Health.

12

WHAT PRACTICES BY CLINICIANS AND THE PUBLIC PREDISPOSE TO THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE?

KEY POINTS

Some antimicrobial agents are more selective for resistance than others

Selection pressure varies with the dosage and duration of therapy

Unnecessary antimicrobial use selects resistance without any gain

Unnecessary antibacterial use includes therapy of trivial, self-limiting or viral infections and over-long prophylaxis

Public expectations of 'A pill for every ill' encourage over-prescribing

Spread of resistant bacteria is aided by (i) crowding of children and the elderly (ii) increased travel (iii) increased 'bed-efficiency' in hospitals

Increased hospital throughput increases antimicrobial use and selection for resistance

Antibiotic use fuels the evolution and spread of resistance. Health care practitioners and the public carry a responsibility for this situation. Claims that the *entire* responsibility lies elsewhere, for example with veterinary antibiotic use, do not withstand scrutiny, as widespread resistance occurs to antibiotics that have never been used outside man (eg third-generation cephalosporins) and in pathogens that are specific to man (eg *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*). This is not to absolve veterinary use, which is a major factor in promoting resistance among enteric pathogens and, perhaps, enterococci, but it is important to stress that the whole responsibility cannot be passed to an other group.

Ultimately, resistance is an inevitable consequence of the use of antimicrobial agents. Nevertheless the practices of prescribers and consumers affect the rate of this evolution. Key factors are:

i)   *total amount of antimicrobial usage*
ii)   *drugs used*
iii)   *dosage regimens*
iv)   *frequency of cross-infection with resistant organisms*
v)   *public behaviour and social conditions*

12.1 TOTAL ANTIMICROBIAL USAGE

The greater rates of resistance in units with heavy usage of antimicrobial agents have been described already (Section 11), but usage and resistance rates also vary from country to country. The USA and Japan together have about 10% of the world population but account for over 60% of the world market in antimicrobial agents. Both countries have high rates of antimicrobial resistance in many common pathogens.

Belgium and the Netherlands have similar populations and standards of living to each other, but the value of the Belgian antibacterial market is roughly double that in the Netherlands ($4.5 billion compared with $2.5 billion). Rates of resistance and particularly of MRSA are lower in the Netherlands than in Belgium.

Considerable geographical variation in antimicrobial prescribing is apparent within the UK, with prescribing in some regions almost double that in others (Figure 5). Rates of resistance also vary between regions. For example, annual rates of trimethoprim resistance in *Escherichia coli* from blood and CSF in East Anglia have ranged between 12.2 and 20.0% from 1989 to 1997; whereas those for isolates from North West Thames ranged from 21.7% to 34.7% (Speller, Johnson, Livermore, personal communication). As yet, there has been little effort to correlate data sets on prescribing and resistance, but the subject is now being given priority within the PHLS Antimicrobial Resistance Programme (Section 17).

12.1.1 OVER-THE-COUNTER AVAILABILITY

In the UK, all antibacterial agents are prescription-only medicines (POM), although certain antiviral agents (aciclovir) and antifungal agents (fluconazole and remedies for athlete's foot) can be authorised by a pharmacist.

Antibacterial agents also have POM status in most of Europe and North America, although these regulations appear to be widely flouted, for example, in Spain, where antibacterial agents can be bought in most pharmacies without a prescription. This easy availability may explain why Spain has a high rate of penicillin-resistant *Streptococcus pneumoniae*; caution must be applied in making a direct connection – Hungary had major and early problems with penicillin-resistant *Streptococcus pneumoniae*, in spite of enforcement of POM status for antimicrobial agents [61].

Antibacterial agents can be bought openly without prescription in many developing countries, in SE Asia, Africa and Latin America. Worse, antimicrobial tablets can be bought singly and may be of low potency. The resulting combination of heavy usage and underdosage exerts considerable selection for resistance. In a study of antibiotic misuse in diarrhoea in Mexico, 72% of those self-administering antibiotics used an inappropriate drug or an incorrect dosage [136].

| 12.2 | FACTORS RELATING TO PARTICULAR ANTIMICROBIAL AGENTS |

The likelihood of selecting resistance depends on the antimicrobial agent. Some drugs select resistance readily others do not. Resistance can be selected in the target pathogen or commensal bacterial flora, which are a reservoir of future opportunists.

12.2.1 AGENTS SELECTING RESISTANCE IN THE TARGET PATHOGEN

Agents that are prone to select resistance should be avoided unless there is no alternative. Key examples are shown in Table 20.

In some cases selection can be prevented by using antimicrobial agents in combination. This is the logic behind the triple combinations (of rifampicin, isoniazid and ethambutol) used in tuberculosis therapy. Resistance emerges if any of these agents is used alone, but not if they are used together. On the other hand – and for reasons that remain unclear – the combination of cephalosporins with aminoglycosides does not reduce the emergence of mutational cephalosporin resistance in *Enterobacter* bacteraemia, although it may improve the clinical outcome [15].

Drugs that readily select mutational resistance generally should be avoided, but this is not always possible. For example, *Pseudomonas aeruginosa* infections in cystic fibrosis patients cannot be bacteriologically cured and the organism can achieve resistance, by mutation, to any of the relevant antibiotics [137–139], with the possible exception of meropenem. In other cases, eg MRSAinfections in the community, a clinician may be forced to used fusidic acid or rifampicin despite the risk of mutational resistance, as no alternative oral therapy is available.

TABLE 20	ANTIBACTERIAL AGENTS PRONE TO SELECT RESISTANCE BY MUTATION

ANTIBACTERIAL AGENT	BACTERIA LIKELY TO DEVELOP RESISTANCE
Rifampicin	All species
Fusidic acid	Staphylococci
Quinolones	Staphylococci, *P. aeruginosa*
Cephalosporins*	*Enterobacter* and *Citrobacter* spp

*Fourth-generation agents are possible exceptions.

12.3 DISTURBANCE OF THE NORMAL BACTERIAL FLORA AND RESISTANT SUPER-INFECTION

Antibiotics used against pathogens may select resistance in the commensal bacterial flora, whose members represent future opportunists. Those with underlying disease or whose immune system is impaired are prone to suffer repeated opportunist infections and even otherwise healthy individuals may develop an undesirable microflora (eg vaginal thrush) following protracted antimicrobial chemotherapy. The choice of antimicrobial has a profound effect on these microbial successions.

The gut is the main site for selection of resistance in the commensal flora, for the simple reason that it contains a huge density of organisms. However, selection may also occur on the skin and it has been noted that quinolones are excreted in human sweat. This may explain the rapidity with which quinolone resistance has emerged in staphylococci [140].

12.4 SELECTION OF RESISTANT COMMENSAL BACTERIA

In one study to analyse the influence of therapy in the community on the flora of patients with respiratory tract infections (RTI), 189 paired faecal specimens were collected before and after antibacterial (n = 129) and symptomatic (n = 60) treatment. The specimens were examined for isolates resistant to amoxycillin, apramycin, ciprofloxacin, nalidixic acid, neomycin, nitrofurantoin, oxytetracycline, sulphamethoxazole and trimethoprim. A significant increase (from 50% to 64%, p <0.05) in the prevalence of resistance to amoxycillin was observed in the group receiving antibacterial agents, but not in the group treated symptomatically. Amoxycillin and doxycycline therapies contributed to increased resistance to amoxycillin and oxytetracycline, respectively. The *Escherichia coli* isolates obtained post-treatment from the group receiving antibacterial agents not only had significantly increased resistance to amoxycillin (from 15% to 23%), but also to neomycin (from 2% to 6%, p <0.05). Cross-resistance also was apparent to neomycin, apramycin and streptomycin [141].

A second example of the selective role of prior therapy is that, where a hospital patient develops an *Enterobacter* bacteraemia, the organism is much more likely (70% compared with 20%) to be cephalosporin-resistant if prior cephalosporin therapy has been given [15].

A third and final example of this type of selection concerns enterococci. These are inherently resistant to cephalosporins and quinolones and increasing use of these drugs is a likely factor behind their rise in importance as pathogens. In addition, enterococci are increasingly often resistant to glycopeptides. A case-control study showed that use of oral vancomycin (p = 0.003) or cephalosporins (p = 0.03) and

prolonged hospital stay (p = 0.02) were significant risk factors for gastrointestinal carriage of vancomycin-resistant, gram-positive cocci, including enterococci. Other previously suggested risk factors, such as location of the patient and the presence of central venous or arterial lines, were discounted. Limiting the usage of glycopeptides and cephalosporins is likely to be the most effective way to prevent and control the spread of glycopeptide-resistant enterococci [142].

12.4.1   SELECTION OF RESISTANT SUPER-INFECTION

The organisms discussed in the preceding section – multi-resistant gram-negative rods and enterococci – are harmless so long as they remain in the gut and act as pathogens only when they invade some other site. Occasionally, antibiotic therapy may favour organisms that cause super-infection. The importance of fungi in this role has been discussed already and vaginal thrush is a frequent and undesirable consequence of antibacterial therapy.

Clostridium difficile is a further example of an antibiotic-selected pathogen and is a major and increasing cause of antibiotic-associated outbreaks of diarrhoea in the elderly in hospitals and nursing homes. Infection is particularly associated with prior use of cephalosporins (whether oral or intravenous [143]) or clindamycin and is much rarer in those who receive ß-lactamase inhibitor combinations or penicillin, trimethoprim or gentamicin [144].

It is perhaps significant that cephalosporins feature in so many of the examples of selection discussed in this section. There is a widespread perception – although one that is difficult to substantiate statistically – that these drugs have played a key role in selecting resistance in the past decade.

12.5   REGIMEN

The selection pressure exerted by an antimicrobial agent varies with the dosage and treatment period, as well as with the compound itself. The optimum duration of therapy is finely balanced – and is poorly defined for many combinations of organism and antimicrobial agent.

12.5.1   DURATION AND DOSAGE

Excessively protracted therapy increases the selective pressure for resistance in the commensal flora. The likelihood of selecting fungal infections or gut infection with *Clostridium difficile* is also increased. On the other hand, excessively brief therapy is likely to allow the least susceptible members of the infective population to survive and to re-establish the infection. The emergence of multi-drug resistance in *Mycobacterium tuberculosis* provides a graphic example of this latter risk, being particularly associated with underdosage arising from poor compliance with protracted and distasteful regimens [89].

Single-dose ('one shot') therapy in sexually transmitted disease provides a second good example of the potential for resistance through underdosage. The advantage of such regimens is that they obviate the need for follow-up, which is valuable because many patients fail to re-attend at genitourinary medicine clinics. However, single-dose regimens give antibiotic levels that are only just adequate against many *Neisseria gonorrhoeae* strains, with the result that small decreases in susceptibility may be progressively selected. MICs of penicillin for typical isolates of *Neisseria*

gonorrhoeae have increased from 0.007 mg/l in the l940s to 0.12–0.25 mg/l nowadays and the recommended dose of benzylpenicillin or ampicillin for single-shot therapy has increased 50-fold. Had high-dose therapy been used earlier, this progression might have been prevented; instead, clinicians must now use the maximum dose of ampicillin together with probenecid to slow down its excretion.

12.5.2   PHARMACODYNAMICS

The relationships between dosage regimen, pharmacokinetics and therapeutic efficacy are only now beginning to be understood for many antimicrobial agents. This is leading to dramatic changes in regimens. Thus, aminoglycosides are now given as a single large daily dose rather than split into three smaller doses per day, as was the practice for the preceding 25 years.

This new science of 'pharmacodynamics' has concentrated on optimising bactericidal activity and minimising toxicity, not on minimising resistance. Nevertheless, it is reported that the likelihood of selecting quinolone-resistant mutants is inversely related to the serum peak level of these drugs, whereas the bactericidal activity relates to maintaining the drug level above the MIC for the bulk of the population [145]. Similarly, third-generation cephalosporins do not select resistant *Enterobacter* in the urine, where they are concentrated to very high levels, but are selective in the blood and lungs, where the levels achieved are lower [8].

Drugs with a long half-life in the body deserve a particular mention, as there are strong economic pressures for their development. Examples include the macrolide, azithromycin, the cephalosporin, ceftriaxone and a quinolone, rufloxacin, which is not yet available in the UK. Their long half-life allows infrequent dosing, which improves compliance and permits out-patient intravenous administration, if needed. The potential (but unproven) risk is that surviving bacteria are exposed to sub-therapeutic drug levels for protracted periods and these may be ideal for the selection of resistance. These aspects need further research.

12.6   ROUTE

Some routes of administration carry specific resistance risks. Both topical and oral uses deserve mention.

12.6.1   TOPICAL ANTIMICROBIAL AGENTS AND DISINFECTANTS

Topical usage of antimicrobial agents amounts to only 1% of systemic use, amounting to 4.9 tonnes in 1997, as compared with 470 tonnes for systemic use (Table 5, data kindly supplied by IMS HEALTH, Maxims Database). The use of topical antimicrobial agents has long been discouraged, on the grounds that it carries a particular risk of selecting resistance. Nevertheless, there is no obvious reason why this mode of use should be especially selective and much of the concern is based on old observations for *Staphylococcus aureus* with penicillin. This concern may be overdone, considering that skin staphylococci develop resistance to tetracyclines, macrolides and quinolones even when these are given orally [146]. It is even arguable that topical usage should exert less selection for resistance than systemic usage, as members of the gut flora are not exposed and as the high local drug levels should overwhelm many mutational resistances.

Some topical antibacterial use is strongly defensible, for example:

i) *the treatment of eye and ear infections*
ii) *the use of sulphonamides with silver nitrate to prevent and treat burn wound infections*
iii) *the use of mupirocin to eliminate colonisation and superficial infections caused by MRSA*

In the case of eye infections, other modes of administration give poor delivery. Moreover the drugs most commonly used – bacitracin, chloramphenicol, neomycin and polymyxin – have little role to play in systemic infections, although they may select for multi-resistance plasmids. In the case of sulphadimidine on burn wounds, the drug is used in combination with silver nitrate and the emergence of resistance in *Pseudomonas aeruginosa,* which is a key pathogen in this setting, is much less than to systemic antimicrobials [147]. Mupirocin must be used topically, because it is metabolised if given systemically. It is invaluable for elimination of MRSAcarriage, achieving permanent eradication whereas earlier disinfectant regimens had only a temporary effect [148]. The only other regimens claimed to be as effective as mupirocin in this role are topical polymyxin, bacitracin and fucidin [149] or topical triclosan, fucidin and bacitracin, with oral rifampicin and ciprofloxacin [150]. These latter regimens employ valuable systemic agents and topical mupirocin seems a preferable alternative. Nevertheless mupirocin can be abused, eg by being given as blanket treatment/prophylaxis to staff and patients on wards where infection is present [151].

Other topical usage of antimicrobial agents may be less defensible. Topical antiseptics and disinfectants may be more appropriate alternatives for minor skin lesions than the antibiotic ointments that are commonly prescribed at present. Clayton *et al* [152] reported that aluminium acetate was as effective (67%) in curing otorrhoea as was gentamicin. Moreover, whereas 12 of 139 ears yielded gentamicin-resistant isolates at presentation, none had isolates resistant to aluminium acetate. Eady and Cove [146] advocated topical benzoyl peroxide in preference to topical antimicrobial agents in the treatment of mild acne, whilst noting that oral tetracyclines or 3-cis retinoic acid are preferred for severe cases.

It should be added that bacteria can acquire resistance to many disinfectants as well as to antimicrobial agents and that these resistances can be linked. Disinfectants may select resistance to antibacterial agents and vice versa. For example, MRSAare commonly much more resistant to quaternary ammonium compounds (eg cetrimide), benzalkonium chloride, chlorhexidine, povidone-iodine and propamidine isoethionate than are methicillin-susceptible *Staphylococcus aureus* strains [153]. Likewise, multi-resistant gram-negative bacteria are often more resistant to quaternary ammonium disinfectants and chlorhexidine than are antibiotic-sensitive strains [153]

12.6.2   ORAL ANTIMICROBIAL AGENTS

For obvious reasons, oral antimicrobial agents are preferred to parenteral for community use. However, if they are incompletely absorbed, they place a particularly direct selection pressure on the gut microflora. The implications of this were discussed in Sections 12.2–12.3.

CURRENT VARIATIONS IN DOSAGE AND DURATION OF THERAPY

Whilst the dosage and duration of therapy are key factors in modulating selection pressure, it is apparent that regimens vary hugely from hospital to hospital, often with no underlying rationale. A recent *ad hoc* review of local prescribing guidelines showed that basic information on dose and total length of course was often omitted (Table 21).

TABLE 21

INFORMATION AVAILABLE IN 23 SETS OF PRESCRIBING GUIDELINES FOR ACUTE OTITIS MEDIA, COLLECTED FROM PHLS LABORATORIES

ANTIBACTERIAL AGENT	DOSE (mg)	FREQUENCY (/day)	TOTAL (days)	NUMBER OF GUIDELINES* (total = 23)[†]
Amoxycillin	250	3	5	2
		3		1
	500	3	5	5
	500	3	7	1
	500	3		5
				5
Co-amoxiclav	500	3	5	1
	500	3		1
Ampicillin				1
Penicillin V				1

*The right-hand column shows the number of guidelines containing the information, eg amoxycillin 250 mg three times a day for 5 days was recommended by two guidelines and amoxycillin three times a day, but with no indication of dose or total number of days therapy required was advised in one guideline. Empty cells indicate that no information was available in the guideline.
†Three guidelines mentioned that the infection could be viral and that treatment with antibiotics was not warranted; one guideline mentioned that treatment was controversial.
Data source: Weinberg J, Livermore DM, Duerden BI, submitted.

BOX 10

GUIDELINES FOR ANTIMICROBIAL AGENTS SHOULD

- be evidence-based
- be dated
- contain information on the antibacterial agent, dose, frequency and length of course
- indicate the strength of the evidence for the recommendation
- show local variation from national recommendations

SELECTION FACTORS RELATED TO THE TYPE OF CLINICAL USAGE

Necessary use of antimicrobial agents – whether prophylactic, empirical or therapeutic – exerts selection for resistance. The question is always whether the gain outweighs the risk; whether the choice of antimicrobial agent maximises the benefit and minimises the risk. Unnecessary use exerts selection pressure with no gain.

12.8.1   PRESCRIBING UNNECESSARILY OR INAPPROPRIATELY

In community practice – which accounts for 80% of total human use – antimicrobial agents continue to be prescribed unnecessarily and empirically for trivial complaints, where no treatment is necessary, or where culture and sensitivity results could safely be awaited [154–163]. The use of empirical antimicrobial agents in upper respiratory tract infections is a key concern, as it accounts for 50% of all human usage. Common indications for this prescribing are sore throats, otitis media, sinusitis and virtually any combination of cough, wheezes, chest pain, discoloured sputum or dyspnoea.

Penicillin continues to be prescribed to patients who present with sore or reddened throats. About 10–20% of these patients have infections with S*treptococcus pyogenes* and may benefit from therapy (Box 6). Even then, many do not. The remaining 80–90% have non-bacterial infections, and do not benefit [164–166]. In the case of otitis media, meta-analyses have shown either no conclusive benefit with antimicrobial chemotherapy or only a slight benefit [27,28] (see Box 5).

While treatment of otitis media or reddened throats may benefit a subset of patients, antimicrobial treatment for less specific symptoms is even commoner and is even less defensible. Mainous *et al* [167] recorded the results of 2144 consultations for 'acute nasopharyngitis' at out-patient facilities in Kentucky, finding that 60% led to antibiotic prescription, 34% to no prescription and 6% to a prescription for an antihistamine or other drug for symptomatic relief. Fewer than 2% of the patients had a secondary diagnosis, such as otitis media, that might justify an antimicrobial agent!

MacFarlane *et al* [158,163] examined the influence of patients' expectations on antibiotic treatment of acute lower respiratory tract infection (RTI) in general practice and found that, in nearly a fifth of these cases (126/581), physicians had prescribed an antibiotic where they thought it was 'probably or (rarely) definitely not indicated'. As discussed below (Section 12.10) this unnecessary use partly reflected patient pressure.

In the same context, the Drug Utilisation Research Unit (Queens University Belfast) noted in its evidence to the House of Lords Select Committee [168] that 'a survey of 21,400 patient encounters revealed that, for upper RTI (70% of which is viral in all age groups), an antimicrobial agent was prescribed for over 80% of patients, including 70–80% of those not actually seen by the doctor. Even where the diagnosis was coryza (common cold), 42% of patients were prescribed an antimicrobial'. A number of justifications for such prescribing are shown in Box 11.

BOX 11	**JUSTIFICATIONS FOR PRESCRIBING**

'I've done it for the past 20 years'
'Just in case'
'To prevent secondary infection' (in a viral disease)
'It relieves my worry'
'Antibiotics do no harm'
'The patient or mother demands it'

The UK is not isolated from other countries where overuse of antibiotics is often far worse. In a survey of 1659 Mexican households, an antibiotic was used in 37% of 287 diarrhoeal episodes [136], whereas this therapy was only justified (on the basis of blood in the stool) in 6%.

In China, Hui *et al* [169] evaluated 750 cases of acute respiratory infection treated by 100 health care workers; 97% of the health care workers were identified as misusing antibiotics. Misuse often entailed use against infections that were presumably viral, but other examples included prescribing combinations of incompatible agents. Patients with confirmed bacterial infections almost always (98.5% of cases) received antibiotics, but in 63% of cases, the drugs given were inappropriate. Another study from China showed that 98% of children attending the out-patient department of Beijing Children's Hospital with symptoms of the common cold were given an antibiotic and that more than one third of these patients had been taking antibiotics prior to attending [170].

A review of antibiotic use at a teaching hospital in Thailand [171] found that 307 of 690 patients had received antibiotics in two 2-week periods and that the drugs given were entirely appropriate for only 27 of these patients. The main problem was use of antimicrobial agents without evidence of infection.

12.8.2   PROPHYLAXIS AND PERI-OPERATIVE ADMINISTRATION

Prophylactic use of antibiotics – to prevent rather than treat infection – carries a selection risk. This is increased where the prophylaxis is prolonged. Antimicrobial agents are used prophylactically in surgery, particularly to prevent infections arising from spillage of the gut bacterial flora into the abdominal cavity. Antimicrobial prophylaxis is also used in contacts of meningococcal disease cases.

12.8.2.1   Prolonged and unnecessary surgical 'prophylaxis'

Excessively long antimicrobial prophylaxis of surgical infection appears to be the principal reason for 'inappropriate' administration in current surgical practice. In reality a single prophylactic dose usually is adequate (Box 12).

A procedure evoking strong debate is selective gut decontamination [172]. This entails giving an oral mixture of non-absorbed antimicrobial agents (polymyxin, tobramycin and amphotericin) to reduce the gram-negative gut flora and prevent fungal overgrowth. The likelihood of aspiration pneumonia is thereby reduced, but concern has been expressed about selection of resistance in the longer term.

The use of antibacterial agents in expectant mothers known to carry group B streptococci deserves mention. There is a risk that contamination of the infant at birth will lead to septicaemia or meningitis. This risk is greatest if delivery is by the vagina rather than caesarean section, if there has been a long delay between rupture of the membranes and birth and if the mother has undergone numerous investigative procedures preterm. Attempts to eliminate vaginal carriage with amoxycillin or penicillin V are commonly unsuccessful and current American recommendations seem reasonable: to give carriers 2 g of ampicillin or 3 g of penicillin at induction of labour followed by 1 g of ampicillin 4-hourly or 1.5 g of penicillin 6-hourly until delivery [173].

12.8.2.2   Prolonged peri-operative prescription

Failure to distinguish infection and inflammation may misguide surgeons to continue administering antibacterial agents for longer than necessary. The concept for shortening courses of antibiotic administration is supported by a forum of experts [174]. The majority of these experts also favoured a moving away from therapeutic courses of fixed duration, towards tailoring the duration of administration to the intra-operative findings. In general, this change would shorten treatment courses. Specific recommendations are shown in Box 12.

BOX 12

RECOMMENDATIONS FOR PROPHYLAXIS IN SURGERY

CONTAMINATION: single-dose per-operative prophylaxis (eg in gastroduodenal peptic perforations operated within 12 hours, traumatic enteric perforations operated within 12 hours, peritoneal contamination with bowel contents during elective or emergency procedures, early or phlegmonous appendicitis, or phlegmonous cholecystitis).

RESECTABLE INFECTION: per-operative and 24-hours postoperative antibiotics (eg in appendicectomy for gangrenous appendicitis, cholecystectomy for gangrenous cholecystitis, bowel resection for ischaemic or strangulated 'dead' bowel without frank perforation).

ADVANCED INFECTION: 48 hours to 5 days therapy, based on operative findings and the patient's condition (eg in intra-abdominal infection from diverse sources).

SEVERE INFECTION WITH A SOURCE THAT IS NOT EASILY CONTROLLABLE: longer administration periods of antibiotic may be necessary (eg in infected pancreatic lesions) [175].

12.8.3   EMPIRICAL THERAPY

Empirical antibacterial therapy should be given when bacterial infection is suspected and *poses a sufficient health risk to demand immediate treatment*. Clear examples include fever of unknown origin in neutropenic patients [174], pneumonia, meningitis and tuberculosis.

In reality, empirical therapy is used far more widely. In community practice, microbiological examination of specimens is rarely undertaken before initiating therapy and in hospitals therapy that begins empirically remains so because of difficulty in obtaining a specimen or disinclination to do so. Thus, in one recent PHLS study of hospital-acquired infections, only 34% of clinically defined chest infections and 23% of pneumonias yielded cultures positive for pathogenic bacteria [176]. These percentages reflect the difficulty of obtaining a good sputum specimen. Similarly low proportions for cultures from wound swabs reflect pressures to save costs or time.

Specific problems with empirical therapy which exacerbate selective pressure are:

i)   *it is likely to be given to patients who do not have bacterial infections*
ii)   *inappropriate antibiotics may be selected*
iii)   *it is common practice to use broad-spectrum agents or combinations to cover all likely pathogens [177]*

Empirical regimens should be based on a knowledge of the likely pathogens and their antimicrobial susceptibilities. Thus, good empirical therapy depends on good LOCAL susceptibility data (see Section 17). Even if available, this often fails to be communicated from laboratories to the wards, let alone to primary care physicians. Yu *et al* [177] examined empirical therapy given to bacteraemia patients in the USA and found that 34% of prescriptions were unacceptable and that the reasoning behind the choice was flawed in 57% of cases. There is little reason to suppose that the situation is better in the UK.

A common example of inappropriate empirical therapy is the use of present-generation quinolones (such as ciprofloxacin) in community-acquired lower RTI. These drugs have only moderate activity against *Streptococcus pneumoniae*, which is

the most serious pathogen at this site. Moreover, their use is prone to select for *Streptococcus pneumoniae* mutants with further elevated resistance and this risks undermining new anti-gram-positive quinolones (such as grepafloxacin, moxifloxacin and trovofloxacin), even before they are launched. Nevertheless, respiratory tract infection is the commonest single reason for prescribing ciprofloxacin in the community (data from IMS) accounting for about 40% of all the use of the drug.

The use of vancomycin as a component in empirical therapy (eg in febrile neutropenic patients) is a concern and to be discouraged. Vancomycin is the *last* effective drug against many gram-positive cocci and its use – where not absolutely necessary – adds an undesirable selection for resistance. Moreover, it is highly doubtful whether the early use of vancomycin in these regimens is valuable. The likely pathogens in neutropenic patients are α-haemolytic streptococci and coagulase-negative staphylococci. The former are sensitive to penicillins and the latter do not give rapidly progressive disease. If a ß-lactam-resistant coagulase-negative staphylococcus is isolated, vancomycin can be added at a later stage without putting the patient at risk [178].

Empirical therapy should aim to minimise the selection pressure for resistance. Herein, though, lies the problem: the need to cover a wide range of likely pathogens with disparate antibiograms promotes use of broad-spectrum agents, which exert a wide selection pressure. To minimise this pressure, it is desirable that treatment is switched to a narrow-spectrum therapy once laboratory data for the pathogen become available. Unfortunately, this change is notoriously easier to advocate than to achieve: physicians generally prefer to continue the broad-spectrum agent if the infection is resolving, rather than to switch to another agent on the basis of laboratory data. This situation may be tractable to the introduction of rapid microbiological testing (Section 16.1.3).

12.8.4 PROLONGED OR REPEATED ANTIMICROBIAL THERAPY/PROPHYLAXIS

Long-term or frequently repeated antibacterial therapy or prophylaxis in chronic or recurrent infections can exert considerable selection pressure both on the target pathogen(s) and on the commensal bacterial flora. Relevant examples include the treatment of:

i)   *Tuberculosis*
ii) *Pulmonary colonisation and bacterial infection in patients with cystic fibrosis*
iii) *Recurrent urinary tract infection in children*
iv) *Chronic obstructive airways disease (COAD)*
v)   *Acne*
vi) *Helicobacter pylori infection*

Prolonged therapy is essential and curative in the case of tuberculosis and exerts less selection for resistance than might be feared, as the triple drug combinations used militate against overgrowth of resistant mutants and as two of the key agents (izoniazid and ethambutol) are not active against other micro-organisms.

Antibacterial therapy in cystic fibrosis patients is not curative of pulmonary infection, but is associated with a reduction in bacterial load and an amelioration of the symptoms. However, repeated treatment is strongly associated with resistance. Early infections in these patients are with *Staphylococcus aureus* and *Haemophilus influenzae* and are eradicable, but later infections are with *Pseudomonas aeruginosa* and

(increasingly) *Burkholderia cepacia*. Despite *in-vitro* susceptibility, *Pseudomonas aeruginosa* infections generally cannot be eliminated, and repeated cycles of antibacterial agents are given. Resistance emerges by mutation, virtually regardless of the antibacterial agent. Strangely, antibacterial agents that appear inactive *in vitro* still continue to yield some clinical improvement in the patient [179]. *Burkholderia cepacia* is even more resistant than *Pseudomonas aeruginosa* and infections are often untreatable [180]; its rise to importance may reflect the increasing ability of physicians to control *Pseudomonas aeruginosa* infections, or the emergence of new strains.

Recurrent urinary tract infection in children is commonly associated with reflux related to anatomical abnormalities and a full examination should be undertaken before long-term prophylaxis is initiated.

The use of antibiotics in chronic obstructive airways disease (COAD) remains controversial, except where a frank pneumonia is present. Fagon and Chastre [181] concluded that a subset of patients did benefit, but that many recover without therapy. This conclusion is in keeping with a meta-analysis by Saint *et al* [182], who noted that the antibiotic-associated improvement was clinically significant in patients with low base-line peak flow rates. The major pathogens of urinary tract infections (*Escherichia coli*) and COAD (*Haemophilus influenzae* and *Moraxella catarrhalis*) do not readily mutate to resistance during therapeutic drug exposure but have accumulated resistance over time by acquisition of foreign DNA.

The treatment of acne – where minocycline therapy often lasts for a year or more – has received remarkably little microbiological analysis or comment, but does use a broad-spectrum antibacterial agent which would be expected to exert major selection pressure on the commensal flora [183].

The role of *Helicobacter pylori* in gastric ulcer disease has been recognised over recent years and the efficacy of antibacterial therapy has been accepted. The emergence of resistance has been recognised, notably to metronidazole [184], although its frequency is unclear – the difficulties of sampling and testing mean that microbiological investigation is rarely undertaken.

12.9   CROSS-INFECTION AND THE SPREAD OF RESISTANCE

The 'resistance problem' encompasses two overlapping problems; first, the initial **emergence** of resistant strains and secondly, the **spread** of these strains or their genes. The relative importance of these processes varies among species and MRSA and cephalosporin-resistant *Enterobacter* spp provide contrasting examples.

The initial evolution of MRSAis rare but, having evolved, they have a remarkable facility to spread. Thus just two strains, EMRSA15 and 16, are widely prevalent in the UK at present [151]. Here, the problem is cross-infection, and is most likely to be ameliorated by infection control measures, not changes in antibiotic policy.

With cephalosporin resistance in *Enterobacter* spp the source is often the patient's own gut bacterial flora and the species has a ready ability to mutate from cephalosporin-susceptible to cephalosporin-resistant. Consequently, infections are more likely to be resistant in those who have received prior cephalosporin therapy [15] and the best chance of control lies with an effective antibiotic policy.

12.9.1   SPREAD OF RESISTANT BACTERIA WITHIN HOSPITALS

Where, as with MRSA, resistance is essentially a cross-infection problem, several factors can exacerbate the situation. These include:

i) *Poor hygiene within hospitals, and poor compliance by staff with hand-washing procedures*
ii) *Increased movement of patients within hospitals*
iii) *Repeated transfer of colonised or infected patients between hospitals and nursing homes*

MRSA are not the only multi-resistant pathogens able to spread readily among patients. Major outbreaks of infection with multi-drug resistant gram-negative pathogens have also been reported. For example, there was a major single-strain outbreak of multi-resistant klebsiellae in the Grampian Region of Scotland. Between 1992 and 1994, 283 patients were involved at six establishments, ranging from a tertiary referral centre to cottage hospitals [185]. Sporadic clusters of infections with multi-resistant *Acinetobacter* spp have occurred in some British hospitals since 1977 [186].

The means of outbreak control are well-known and comprise some combination of:

● transfer of infected or colonised patients to isolation cubicles
● cohort nursing
● emphasis on the importance of hand-washing before and after patient contact and when handling case notes
● the use of disposable aprons and gowns during patient contact

These practices are increasingly constrained by budget pressures and by the need to achieve maximum efficiency in bed use, which results in those colonised with resistant bacteria being moved around hospitals, increasing the likelihood of spread.

12.10   PUBLIC BEHAVIOUR AND SOCIAL CHANGE

Changing lifestyles impact on the resistance problem, with key factors as follows:

i) *Public expectation of receiving antibiotics for any infection*
ii) *Travel*
iii) *Overcrowding in long-term and day-care facilities*

12.10.1   PUBLIC DEMAND FOR ANTIBIOTICS

Excessive prescribing of antibacterial agents for trivial and non-bacterial infections in primary care partly reflects 'consumer' pressure. Patients should be empowered and encouraged to take control of their own health care but, unless they have access to appropriate advice, this may lead to demand for inappropriate treatment, such as antibiotics for the common cold, 'flu', or sore throat. Failure to prescribe may lead to the patient being dissatisfied.

Macfarlane *et al* [158] reviewed questionnaires from 787 of 1014 patients who had recently presented to GPs with acute lower respiratory tract illness [163]. The GPs also completed a case-record form for each patient. Of the 787 responders, 662 thought their symptoms were caused by infection and 656 thought that an antibiotic would help; 564 wanted an antibiotic, 561 expected one and 146 requested one. These desires, requests and demands were unrelated to the severity of the symptoms; 587 of the patients actually received an antibiotic although the doctors thought these

were 'definitely indicated' in only 116 cases and 'definitely or probably not indicated' in 126. Patient pressure most commonly influenced the decision to prescribe when the doctor thought it to be unwarranted: patients who did not receive an antibiotic were prone to express dissatisfaction and were twice as likely to re-attend, for the same episode, as satisfied patients.

Nevertheless, as the same authors note, 'GPs can over-estimate patients' expectations. A quarter of patients received antibiotics when they stated that, before the consultation, they had not wanted antibiotics!'.

Britten [187] also makes the point that patients cannot take all the blame for over-prescribing.

TABLE 22   **GPs' CERTAINTY ABOUT THE NEED FOR ANTIBIOTICS WHEN PRESCRIBING FOR LOWER RTI**

	ANTIBIOTIC PRESCRIBED 206/787=26%	ANTIBIOTIC NOT PRESCRIBED 581/787=74%
GP's view on whether antibiotics were indicated (% of group)		
Definitely indicated	116 (20%)	2 (1%)
Probably indicated	339 (58%)	0
Probably not indicated	120 (21%)	99 (48%)
Definitely not indicated	6 (1%)	105 (51%)
Non-clinical factors influencing decision to prescribe	249 (44%)	6 (3%)
Non-clinical factors influencing prescribing (% of group)		
Patient's expectation or 'pressure'	133 (53%)	2
Social factors for patient	66 (27%)	0
'My experience is that patient will otherwise re-attend'	53 (21%)	1
Work pressure on doctor	18 (7%)	0
Other	45 (18%)	4

Data source [158]

Poor concordance is a further problem. Its importance as a cause of selecting resistance in tuberculosis therapy has been mentioned already. More generally, patients are prone to stop taking an antibiotic once they 'feel better', leading to the survival of a few more resistant members of the infective population. These may regrow, re-asserting the infection and perhaps spreading. Baquero claims a 91% concordance with full courses of antibiotics in the UK, compared with 58% in Spain [188], but the provenance of these data is open to question. Moreover concordance is likely to vary with the specific drug, convenience of the regimen, the patient's attitude and the speed at which the symptoms resolved.

Other bad practices, well-known but difficult to quantify include:

● Taking a few antibiotics 'left over' from a previous course when the individual next feels unwell
● Self-prophylaxis against sexually transmitted diseases (STD) or travellers' diarrhoea
● Among STD patients, sharing a single course of therapy between two sexual partners.
● On the other hand, failing to take a complete course of an unnecessary antibiotic mitigates selection pressure on the commensal flora!

12.10.2 TRAVEL

The high rates of antimicrobial resistance in many overseas countries have been noted already. These may reflect greater prescribing, poorer control of infection and over-the-counter availability of antimicrobial agents. Laws on patents and pharmaceutical quality are absent or not enforced in many developing countries and, in some of these, antimicrobial agents are sold by the single tablet, leading to frequent underdosage.

The UK is not isolated from these problems. The PHLS is aware of instances where patients have been hospitalised in Spain and Crete for myocardial infarction and have returned to the UK with multi-drug resistant *Acinetobacter* infections. One such strain, imported with a patient returned from Spain, spread among other patients in an intensive care unit and was associated with three deaths. Similarly, multi-resistant strains with unusual ß-lactamase types have been imported to the UK with patients who had been hospitalised on the Indian subcontinent [189].

Resistant strains of classical pathogens may also be imported, with multi-resistant *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* presenting particular risks. Spread of *Streptococcus pneumoniae* following importation from Spain to Iceland is considered below (Section 12.10.4).

12.10.3 LONG-TERM CARE FACILITIES

The role of nursing homes and other long-term care facilities (LTCFs) as reservoirs of resistant bacteria is an increasing concern in both the UK and the USA, with MRSA presenting the main problem. Elderly and debilitated patients increasingly are shuttled between LTCFs and hospitals, with the risk of MRSA being transferred and then spreading within the LTCFs, where control of infection/colonisation measures are often minimal.

Flournoy [190] examined 301 *Staphylcoccus aureus* isolates from nursing home patients in Oklahoma and found that 70% were resistant to methicillin and 72% to ciprofloxacin. In a point prevalence study in Birmingham (UK), Fraise *et al* [191] recovered MRSAfrom the noses or fingers of 33/191 LTCF residents, although only one had a clinical infection. The same authors found environmental MRSA contamination in most of these establishments, although few environmental samples (12%) yielded the organism. The MRSAstrains resembled those circulating in Birmingham hospitals and risk factors for colonisation included hospitalisation or surgery within the preceding year. Bradley [192] also concluded that most MRSA colonisation of LTCF patients was acquired during hospitalisation, not at the nursing homes themselves. Within the nursing homes, colonisation was persistent, lasting for months or years, despite eradication efforts. These studies argue against transmission within LTCFs being a major problem, but others have reached the opposite conclusion, perhaps reflecting the varying health status of the residents (MRSA does not readily colonise healthy individuals) or the MRSAstrains prevalent in the locale. Thus, Mulhausen *et al* [193] in the USA, noted *acquisition* of MRSAcolonisation in LTCFs, as well as in hospitals [194].

Early discharge of MRSA-colonised patients from hospitals may exacerbate the problem in nursing homes. Eltringham [51] found that the number of new MRSA cases at a teaching hospital in London grew from 140 in 1994 to 400 in the first half of 1995 and that the clearance rate with mupirocin therapy fell from 25% to 5%, apparently because of a decreased mean duration of stay from 55 to 35 days. He noted that 'this increases the likelihood of a reservoir of MRSAin the community'.

Nevertheless, the incidence of clearance – 25% – was less than impressive even with long hospitalisation!

Other multi-resistant bacteria may become disseminated within nursing homes besides MRSA. Flournoy [190] found that 22% of *Enterococcus faecium* isolates from a group of nursing home residents in Oklahoma were resistant to vancomycin and Schiappa *et al* [195] described dissemination of the same multi-resistant *Klebsiella* and *Escherichia coli* strains in both nursing homes and hospitals in Chicago.

Attempts to improve antimicrobial use in the LTCF are complicated by the characteristics of the patient population, limited availability of diagnostic tests and the virtual absence of relevant clinical trials. Nicolle *et al* [196] recommended approaches to management of common LTCF infections and proposed minimal standards for an antibiotic review programme. In developing these recommendations, the authors acknowledged the unique aspects of provision of care in the LTCF.

12.10.4   NON-HEALTH-CARE SETTINGS

Day-care facilities for children are typically crowded, facilitating the spread of colonisation and infection, particularly with resistant *Streptococcus pneumoniae* [197]. The potential problem associated with modern child-care systems, combined with international travel, is best illustrated by the spread of multi-resistant *Streptococcus pneumoniae* in Iceland. Like other Scandinavian countries, Iceland generally has low rates of resistance and until l988, penicillin-resistant *Streptococcus pneumoniae* isolates were virtually unknown. From l989 to l993, however, their incidence rose swiftly until they represented 20% of all *Streptococcus pneumoniae* isolated. This change reflected the spread of a resistant serotype 6 strain that was already prevalent in Spain, where many Icelanders go on holiday. It seems that children were colonised by the strain whilst in Spain and that it then spread among them in the child-care facilities, which most attend. Other (type 23F) multi-resistant Spanish strains of *Streptococcus pneumoniae* have spread to the USA [198] and, again, have disseminated via day-care centres [199].

The spread of resistance in these instances occurred in prosperous societies. In other instances (eg resistant tuberculosis), spread of resistance is often associated with poor social conditions, including homelessness and overcrowding. Overcrowded conditions exist in other environments such as military barracks and prisons; as described above, the spread of colonisation and infection may be facilitated in these circumstances. This in turn increases the risk of spreading resistance.

12.11   SHORT-TERM GAIN AND LONG-TERM COST

Several factors that promote resistance cannot readily be ascribed to **either** the prescriber **or** the consumer but, rather to their interaction with each other and with wider society.

The best treatment for an individual patient now may not be the best for future society, if it selects resistance. This conflict becomes most apparent in those countries where the patient is usually a paying client of the physician, who may argue that he or she should be free to prescribe the most powerful antimicrobial agent, on the grounds that their sole responsibility is to the 'customer'. This argument is less frequently heard in the UK but is still relevant, because resistant bacteria may be imported and because private medicine may increase.

Criticism may more appropriately be levelled at the prescription of the most powerful antimicrobial agent for a minor UTI or RTI than at the same prescription for a patient with nosocomial pneumonia when there are two other patients on the same unit who have a multi-resistant strain which may have spread.

Even more contentious is the question of using an antimicrobial agent, with its contingent selection pressure, in medical procedures that have little or no chance of prolonging life of any quality. There is a small chance that the individual may benefit and a rather greater possibility that later patients may benefit from the knowledge gained, but there is also the threat to a large number of patients whose therapy might be undermined by the selection for resistant organisms. Whilst scientific, this line of reasoning raises profound ethical issues.

12.12 VETERINARY USE OF ANTIMICROBIAL AGENTS AND THE EMERGENCE OF RESISTANCE

Disease is inevitable in farm and companion animals. Moreover, healthy animals can be carriers and asymptomatic excretors of pathogens. Antimicrobial resistance is best documented for farm animal pathogens, where it varies with the animal species, the type of husbandry, environmental pressure, the standard of stockmanship and with the pattern in trade in the animal type. Antimicrobial agents are used extensively to combat disease and such use has also been proposed as a factor in the emergence of resistance in human pathogens.

12.12.1 TYPES OF ANTIMICROBIAL USAGE IN ANIMALS

The three main reasons for using antimicrobial agents in animals are:

i) *therapeutic*
ii) *prophylactic*
iii) *in farm animals only, performance enhancement (growth promotion).*

The animal diseases requiring the most extensive use of antibacterial agents for therapy or prophylaxis are respiratory and enteric diseases of pigs and cattle and mastitis in dairy cattle.

Therapy involves individual animals or defined groups with identified disease. Its justification is not difficult, as disease can cause death or morbidity in the individual animals or groups. Death of animals requires replacement – with inevitable cost – and may also mean the loss of a genetic line or of a much-loved animal.

Prophylaxis aims to contain the spread of infection in herds or flocks and to prevent illness in advance of clinical signs. Prophylaxis of a herd or group of animals is often undertaken after diagnosis of illness in one or more of its members and is based on previous experience of the disease. It is employed when a proportion of animals are diseased during a defined period and when it appears likely that others in the herd will contract the disease if no action is taken.

The third type of usage – performance enhancement – is the most contentious. The performance enhancing (growth promoting) properties of antimicrobial agents were discovered in the late 1940s and are used to improve the productivity of healthy animals by increasing growth rate, feed conversion or yield. Alternative terms include 'growth promoters' or 'digestive enhancers'. The basis of these improvents is not certain, but it is likely that more food is converted to meat and less is 'lost' to the

gut bacteria. Following its original discovery, the practice was widely adopted and became an integral part of feeding systems in the animal industry. Antimicrobial agents are given continuously at sub-therapeutic doses, usually as feed additives, but may also be administered by addition to the drinking water.

The acceptability of using antimicrobial agents as growth promoters varies between countries: in Sweden such use has been banned since 1986; in the UK there are restrictions on the agents that can be used (see Section 12.12.3); in the USA the tetracyclines and penicillins continue to be used, although such use was banned 30 years ago in the UK.

12.12.2 PRESCRIPTION CATEGORIES OF VETERINARY ANTIMICROBIAL AGENTS

The legal requirements for the distribution of animal medicines differ with the individual products. Under The *Medicines (Restrictions on the Administration of Veterinary Medicinal Products) Regulations 1994,* a product cannot be administered unless it has a marketing authorisation (product licence) for treatment of a particular condition in the species. Veterinary surgeons are the primary prescribers in the UK and it is usual for them to both prescribe and dispense, both for food-producing and non-food-producing animals. For food animals, the veterinarian or person acting under his direction may *only* administer a product licensed for food-producing animals. Human-licensed medicines can also be administered for non-food animals.

Prescription-only medicines (POM) may be supplied by a veterinarian for animals under his care, or by a registered pharmacy on a veterinary prescription. Pharmacy only medicines (P) may be supplied by a veterinarian, or sold over the counter from a registered pharmacy under the supervision of a pharmacist. Merchant list products (PML), including antimicrobial agents used as growth promoters, may be sold by veterinarians and registered pharmacies to **any** customer. Legislation controlling medicated animal feed stuffs apply to anyone who incorporates a medicinal product in an animal foodstuff [200]. A medicinal product classified as a POM or PML may be incorporated only if there is a product licence or an Animal Test Certificate providing specifications for incorporation. There are Codes of Practice for both the professional bodies, the Royal College of Veterinary Surgeons and Royal Pharmaceutical Society of Great Britain, and for merchants.

12.12.3 CONCERN AND RESTRICTIONS IN THE UK: 1960 TO THE PRESENT

Concern about the development of resistance as a consequence of veterinary use has been expressed since the 1960s. Inappropriate veterinary use, or use with poor control, promotes the development of resistance. Resistant bacteria selected in animals may be transferred directly to man via the food chain, or may transfer their resistance genes to human pathogens. Concern is sometimes also expressed about the selective effects of antimicrobial residues in food, but this is more tenuous and available evidence suggests that the risk is low or, at least, extremely infrequent [201].

The Swann Committee, whose report [202] resulted in the UK *Medicines Act 1968*, recommended that antimicrobial agents used for growth promotion and available without prescription should be those with little or no therapeutic application in man and animals, and that their usage should be designed not to impair the efficiency of prescribed therapeutic drugs. The Swann Committee did not, however, recommend restrictions on the veterinary use of antibiotics belonging to chemical *families* also

used in man. This became a major concern with the observation that enteric bacteria selected for resistance to the veterinary therapeutic antibiotic apramycin were also resistant to its analogue, gentamicin, which is used for severe infections in man [69,203]. This led to the recommendation in the Lamming Report (1992) [204] that the prophylactic veterinary use of antimicrobial agents giving cross-resistance to drugs used in human medicine should be 'discouraged'. Likewise the Veterinary Products Committee (VPC) recommended that the prophylactic use of 'new' antimicrobial agents should be discouraged, but stated that they would consider each case on its merits.

Others reached similar conclusions elsewhere in the world; in 1994 the WHO Scientific Working Group on the Monitoring and Management of Bacterial Resistance to Antimicrobial Agents [205] stated that 'the use of antimicrobial agents in animal husbandry, particularly for growth promotion and prophylaxis of infection, provides an additional selective pressure'. They recommended that 'the unnecessary use of antimicrobial agents for prophylaxis in food animals should be discouraged and that antimicrobial agents should not be used as a substitute for adequate hygiene in animal husbandry'.

Despite this general concern, the VPC approved the use of enrofloxacin (a fluoroquinolone related to the human drug ciprofloxacin) in animals in the UK at the end of 1993. This approval was given despite specific concern about the rapid emergence of resistance in campylobacters following enrofloxacin use in poultry flocks and despite information from the Netherlands that its use had contributed to the emergence of ciprofloxacin-resistant campylobacters.

12.12.4   PATHOGENS WHERE USE IN ANIMALS MAY CAUSE RESISTANCE IN HUMAN PATHOGENS

The importance of veterinary antibacterial agents in selecting resistance in human pathogens varies with the bacterial species. At one extreme are the salmonellae, where the same resistant strains (currently phage type DT104, see Section 10.5.1) are prevalent in animals and man, and where veterinary usage is strongly implicated in emerging resistance. Veterinary usage is likewise strongly implicated in the emergence of quinolone resistance in *Campylobacter jejuni* (see Section 10.5). At the other extreme are pathogens specific to man, for example *Neisseria gonorrhoeae*, where veterinary usage is irrelevant to resistance. Between these extremes lie more contentious cases, notably that of avoparcin and glycopeptide-resistant enterococci (GRE, see Section 10.2.1). It was first thought that GRE originated in hospitals, but it is now apparent that they are also frequent in community, sewage and animal sources, including farm animals and raw meat purchased from retail outlets in the UK and Europe. Several workers have suggested that this distribution may reflect the use of another glycopeptide, avoparcin, as a growth promoter in the poultry and pig industries [206, 207]. A direct link is difficult to establish, as glycopeptide resistance is transferable among enterococcal strains and so may be seen in others than those where it evolved. Nevertheless, the same GRE strain was isolated from a Dutch turkey farmer and his avoparcin-fed flock [208]. Avoparcin has not been used in the USAand although GRE are frequent in hospitals [209], they are not seen in food or animals.

The EU SCAN (Scientific Committee for Animal Nutrition) investigated the link between GRE and avoparcin use, finding that the data were inconclusive and that further research was needed. Nevertheless the use of avoparcin as a feed additive was suspended throughout the European Union.

12.12.5 FUTURE HUMAN USE OF VETERINARY ANTIBACTERIAL AGENTS

Although some families of antibacterial agents are presently only used in animals, new analogues may be used in man. Thus dalfopristin/quinupristin (Synercid) and everninomycin (Ziracin), which are now under development as agents against MRSA and VRE, are analogues of virginiamycin and avilamycin, respectively, which have long been used as growth promoters. *Enterococcus faecium* strains resistant to dalfopristin/quinupristin have already been isolated from foodstuffs and from at least one patient [210]. GRE resistant to avilamycin are known and are cross-resistant to everninomycin – a drug that has not yet been used in man and which has one of the most impressive spectra of all the new anti-gram-positive agents [211].

The search for new antibacterial agents in these classes undermines the previous distinction between human and veterinary antimicrobial agents drawn by the Swann Committee and by the Lamming Report, and argues against their use as growth promoters.

12.12.6 IMPROVING VETERINARY USE OF ANTIMICROBIAL AGENTS

Veterinary surgeons are involved in preventive medicine as well as in the diagnosis and treatment of disease. They must be aware of developments in farming that may have disease implications for herds or flocks. There have been significant changes to the regulation and use of antimicrobial agents since the Swann Report [202] and there have been wide-ranging changes in agriculture itself.

There is also the not-insignificant influence of farm-assured schemes and the direct influence on agricultural practices by the major retailers on the possible use of group medications. These quality assurance programmes stress the importance of a strong working relationship between producers and their veterinarians. They also teach efficient management practices and proper drug use as a way of improving the safety of the food supply.

Nevertheless, despite the very best husbandry and correct use of appropriate preventive measures, diseases that demand treatment will still occur in groups of animals; for example, summer mastitis in cattle at grass and pneumonia associated with their housing in the autumn.

In the longer term, vaccines for common illnesses should produce the biggest contribution to reduction in the use of antimicrobial agents. Following the recent introduction of new vaccines, there has been a significant reduction in usage of antimicrobial agents in the poultry industry and the virtual cessation of their use in farmed Atlantic salmon [212, 213]. These developments complement the established vaccines (eg rotavirus and K99 vaccine for calves, leptospiral vaccines for dogs, cattle and sheep, also multivalent clostridial vaccines, and vaccines against foot rot, chlamydial and toxoplasma abortion). Their use significantly reduces antibiotic use in animals.

In the shorter term, antibacterial therapy will continue to be needed. In the case of prophylactic use, Hazard Analysis Critical Control Point (HACCP) principles should be applied on each occasion when such prophylaxis is considered. The HACCP approach is much used in the food industry, but equally can be applied on the farm to assist in identifying critical points where disease can be prevented or where its spread can be stopped or reduced. This analysis should consider not only antimicrobial prophylaxis but also other controls, including improvements to husbandry, appropriate use of vaccines if available and even changes to the

management of the farm. More generally, maximum benefit will only be derived from the use of pharmaceutical and biological products in animals if full consideration is given to the manufacturers' instructions, coupled with sound management practices.

Disease control in animals is multi-faceted and the more traditional 'fire-brigade' responses without consideration of preventive measures are no longer acceptable. In general, the use of antimicrobial agents in animals should be governed by the same principles that apply to their use in humans, namely, to circumstances where they can be expected to produce a genuine health benefit.

12.12.7   ANTIBIOTIC USE OUTSIDE MAN AND DOMESTICATED ANIMALS

Antibiotics have uses outside human and veterinary medicine. These uses deserve brief mention because they augment the selection for resistance. In the late 1980s, the salmon farming industry used considerable amounts of tetracyclines and, later, of quinolones. In Norway, this usage peaked at 47 tons of antibacterial agents in 1987, but reduced to 1.5 tons by 1994, reflecting increased regulation, vaccination and the segregation of farmed fish by age [212]. Between 1981 and 1988 there was a 60% chance that a Norwegian farmed salmon would receive antibiotics in any year; by 1994 this likelihood had fallen to 2.3% [213].

Tetracyclines are used in bee-keeping to cure European foulbrood. This use is trivial in the UK, amounting to about 800 hives per annum, each treated with 1 g of tetracycline, from a national total of c. 200,000 hives. A more virulent disease, American foulbrood, is widespread in much of Europe and the USA, where most hives receive tetracycline continuously, giving much greater selection pressure.

Fruit-growers in the Western USA spray their crops with tetracycline or streptomycin to prevent fireblight (caused by *Erwinia amylovara*). Gentamicin is used for this purpose in Mexico. These antibiotics are chemically stable and may enter the food chain, selecting resistance in the bacterial flora of the gut. Farmers in Britain do not spray fruit crops with antibiotics, but sprayed fruit may be imported.

12.12.8   USE OF RESISTANCE GENES IN GENETICALLY MODIFIED FOODS

Antibiotic resistances are convenient markers in genetic engineering ('cloning'), which is increasingly used to introduce genes giving protection against herbicides and insect pests into crop plants. Ciba-Geigy used this strategy to clone resistance to herbicides and to the European Cork Borer into maize [214] and the Advisory Committee on Novel Foods and Processes (ACNFP) reluctantly approved import of this maize into the UK. Applications are pending with the ACNFP for other modified crops containing bacterial genes coding resistance to ampicillin, kanamycin and streptomycin. Supporters emphasise that (i) the resistance genes have no direct consequences in the plants, (ii) we do not know any process whereby the genes could escape back to bacteria, (iii) these resistance genes are widespread in bacteria and (iv) processing destroys the resistance gene, precluding uptake by gut bacteria [215]. Counter-points are: (i) that we continue to discover new mechanisms of gene exchange and cannot discount the risk of gene escape from plants to bacteria; (ii) that crops containing these genes may escape to the wider environment where control will be impossible; and (iii) that the vast number of gene copies per plant and the large areas planted balance the minuscule likelihood of individual gene escape. Even pollen, borne by the wind, will carry the antibiotic resistance genes. International trading treaties seemingly preclude the UK from banning import of crops with these genes, but we underscore the ACNFP's recommendation that developers should delete the antibiotic resistance genes before these crops enter use.

PREVENTING THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

13.1   DO GOOD PRESCRIBING PRACTICES PREVENT OR SLOW THE DEVELOPMENT OF RESISTANCE?

The relationship between antimicrobial control and resistance was assessed by review of selected journal articles from 1988 through 1998. The strength of the existing evidence is assessed in Section 20. Most studies of control or monitoring do not report susceptibility patterns as an outcome measure. Moreover, biases and confounding factors preclude anything more than analysis of the temporal association between antimicrobial use, restriction and resistance pattern. Many of the studies were performed in single institutions and their power to distinguish associations was poor. Co-operative multi-centre studies are needed in which selection and classification biases are addressed prospectively, and where confounding factors are controlled [16, 216].

In a few cases there have been increases in antimicrobial susceptibility following intensive control or monitoring. More generally, intensive antimicrobial control is often associated with a high prevalence of susceptibility and the proportion of susceptible isolates often falls abruptly when this control or monitoring is relaxed or removed.

13.2   SHOULD RESISTANCE DECLINE IF USE OF ANTIMICROBIAL AGENTS IS RESTRICTED?

Whilst the relationship between the use of antimicrobial agents and the emergence of resistance is clear (if circumstantial), its corollary – that resistance should decline if use is restricted – is much less certain. In principle, resistant bacteria should decline following restriction if:

i)   *Possession of resistance causes a direct stress, leaving resistant strains unable to compete in the absence of the drug*
ii)   *Resistant strains are displaced by others with a more valuable trait (eg a greater ability to survive drying or to colonise)*

Strain displacement does occur. Thus, the original UK epidemic MRSA(EMRSA1) of the 1980s is now rarely seen, having been supplanted by EMRSA3, 15 and 16 [217] which may have a greater ability to colonise and invade than EMRSA1. Such displacements have a major bearing on the stability of resistance.

The contention that there is a cost to resistance seems obvious. Replicating large plasmids or diverting up to 4% of protein synthesis into ß-lactamase (as in some cephalosporin-resistant *Enterobacter* strains) ought to reduce the ability to compete in the absence of an antibacterial agent. Nevertheless many routes to resistance appear to impose little burden. Schrag *et al* [218, 219] found that streptomycin-resistant *Escherichia coli* mutants with a ribosome ('protein factory') change initially grew 12–14% more slowly than their sensitive parent strains, but they readily underwent a compensatory mutation, which increased their growth rate to within 6% of that of

the parent. In nature, even these mutants are much rarer than strains with streptomycin-modifying enzymes, which form an even more efficient mode of resistance [220]. More generally, while several studies have found that plasmid carriage reduced bacterial fitness in the absence of an antimicrobial agent [221–223], others have shown that bacteria gradually evolve to regain fitness despite plasmid carriage. In one extreme case, such co-evolution *increased* the fitness of an *Escherichia coli* strain with a tetracycline resistance plasmid above that of its parent strain [224].

Taken together, these examples indicate that evolution favours those mechanisms that place the least burden on bacteria and that, even when a mechanism does impose a fitness burden, repeated cycles of selection yield organisms in which this burden is minimised. Such efficiently selected resistances are unlikely to disappear swiftly once selection pressure is withdrawn.

Mathematical modelling and population genetics have been employed by Bonhoeffer *et al* [225] in the evaluation of most beneficial antibiotic usage policies to minimise resistance. For directly transmitted bacterial infections their model predicts that the long-term benefit of using a given antimicrobial agent, from introduction to ineffectiveness due to resistance, is almost independent of the pattern of use. With two possible drugs it is more beneficial to use both simultaneously (in different patients) rather than alternate cycling between the two. The best option, however, is to treat all patients with both drugs, unless single plasmids carry resistance to both. This support for combination therapy is consistent with current effective practice in tuberculosis and contrasts with experience of widespread resistance in gonorrhoea, usually treated with a single antibacterial agent. The model also predicts that spread of resistance will be considerably faster than its rate of decline if usage ceases. This model also assumes that recovery from infection coincides with termination of carriage and transmission and its applicability is less clear for organisms that are not obligate pathogens and cause nosocomial infections [226]. It should be added that no modelling approach has yet been applied to predict accurately the future course of a resistance problem.

13.3 DOES RESISTANCE DISAPPEAR IF THE USE OF ANTIMICROBIAL AGENTS IS RESTRICTED?

Having reviewed the theory on whether resistance should disappear once an antimicrobial agent is withdrawn, it is appropriate to consider the direct evidence. This suggests individual answers to individual problems, not a general pattern. Moreover, as pointed out by McGowan and Gerding [16], good studies on the relationship between drug restriction and resistance are few and difficult, because of:

i) *Bias (studies where changes are seen are more likely to be reported than those where they are not)*
ii) *Lack of statistical power*
iii) *Confounding variables, such as hygienic precautions adopted concomitantly with drug restriction; and the role of outbreak strains, whether resistant or not*

13.3.1 RESISTANCE TO DISUSED ANTIMICROBIAL AGENTS

Studies of resistance to disused antimicrobial agents are useful as they examine agents where direct selection is no longer significant and where no active steps are being taken to reduce resistance. Streptomycin and chloramphenicol against Enterobacteriaceae provide examples. Neither drug has been used against these organisms for over 25 years, yet a recent survey in London [227] found that 20% of

Escherichia coli isolates remained resistant to streptomycin. High (>20%) rates of streptomycin resistance were also noted world-wide [220], among healthy volunteers in the USA[228] and in the Netherlands [229]. Chloramphenicol resistance is not so frequent, but occurs in 5–10% of *Escherichia coli* isolates [228]. No currently used clinical drug selects direct cross-resistance to streptomycin or chloramphenicol, but factors that may conserve resistance include the following:

i)   *Both resistances are plasmid-mediated and plasmids may determine resistance to other drugs whose continued use exerts a selective pressure. In particular, streptomycin and sulphonamide resistances are often linked [230].*

ii) *The streptomycin resistance gene lies in an integron, a region of DNA adapted to the recruitment of further resistance determinants [116]. These linked resistances may continue to be selected.*

iii) *Non-clinical use may effect a residual selection pressure. Streptomycin is used as a veterinary antimicrobial agent (not a growth promoter) and in some countries – notably the USA – is sprayed on fruit crops, which may be imported to the UK.*

The slow rate at which resistance clears from populations is further illustrated by the work of Smith [231] who examined the incidence of tetracycline-resistant *Escherichia coli* in pigs in the years immediately after 1971, when its use as a growth promoter was prohibited. His results are summarised in Figure 13.

The proportion of pigs carrying tetracycline-resistant *Escherichia coli* fluctuated randomly from 1970 to 1975, without substantial decline. The only more positive sign (as Smith perceived it) was that the proportion of the *Escherichia coli* isolates carrying the resistance determinant on a plasmid gradually fell, from 73% in 1970 to 36% in 1974. Others might view even this change in a more negative light – as indicating co-evolution of the plasmid and the strains to permit efficient retention. Smith concludes by stating that:

'The failure of the prohibition of the growth promoter use of tetracycline to reduce the amount of tetracycline resistant Escherichia coli *in the pig population stresses the fallacy of assuming that the ecological changes brought about largely by the persistent and widespread use of antimicrobials can be reversed simply by resorting to a policy of withdrawal.'*

FIGURE 13   **TETRACYCLINE-RESISTANT *ESCHERICHIA COLI* IN THE PIG POPULATION**
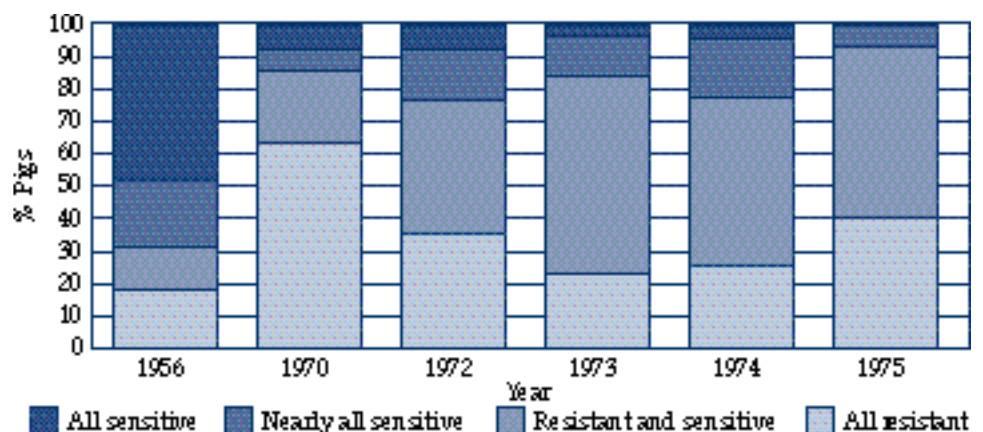
This failure to displace tetracycline-resistant *Escherichia coli* from pigs contrasts with the swift disappearance of *Salmonella typhimurium* DT 29 from bovines following the same 'post-Swann' ban on the use of human antimicrobial agents as growth promoters [67]. It is tempting to speculate (but hard to prove) that the crucial difference lies between a resistance that had disseminated amongst *Escherichia coli*

strains on the one hand and a single-strain outbreak of *Salmonella typhimurium* on the other.

A final example of the slow fall in resistance following disuse concerns sulphonamide resistance in meningococci. This reached 40% in 1986–88, when these drugs were last regularly used for prophylaxis in close contacts of meningitis cases. In the nine subsequent years, when rifampicin and ciprofloxacin have supplanted sulphonamides for chemoprophylaxis, the rate of sulphonamide resistance has fallen to 25% [232].

13.3.2   COMMUNITY EXPERIENCE AFTER CHANGES TO ANTIMICROBIAL POLICY

As McGowan and Gerding note [16], there are few good studies on this topic and investigation is bedevilled by the fact that changes to antimicrobial policy are rarely made in isolation.

One investigation that has caused much comment was by Seppala and the Finnish Study Group for Antimicrobial Resistance [233]. These authors noted an increase in resistance to macrolides amongst *Streptococcus pyogenes* isolates in Finland through the late 1980s and early 1990s, and responded by introducing nation-wide recommendations calling for a reduction in macrolide use for respiratory and skin infections in out-patients. Macrolide prescriptions (doses/1000 population/month) fell from 2.5–3.0 in 1986–90 to 1.4–1.6 in 1992–94, before rising to 1.8 in 1995. The incidence of erythromycin resistance among *Streptococcus pyogenes* isolates was 13.2% in 1990, peaked at 19.0% in 1993, then progressively fell to 8.6% in 1996. The authors assume a causal relationship, but notes of caution should be sounded. First, the original resistance problem may have reflected the clonal spread of a single strain [234], not the dissemination of resistance within the species. Such strain successions commonly occur among *Streptococcus pyogenes* from year to year [235]. Secondly, the same authors [236] reported a concurrent rise in erythromycin resistance amongst *Streptococcus pneumoniae* in Finland, from 0.6% in 1990 to 2.4% in 1995.

There has also been a report of falling resistance to penicillin in *Streptococcus pneumoniae* in Iceland, following a major publicity campaign directed at the public and physicians [237]. Curiously, this finding has not been fully reported in original papers by the study group, but only in reviews and conference presentations. Again, the problem was due to a single clone. This organism was disseminated in day-care facilities, which 90% of Icelandic children attend and the findings may not be generalisable to other countries and situations [238–240].

With the exception of these experiences in Finland and Iceland, no other reports of reduced resistance levels in the community following tightening of prescribing policies have been found, although several reviews advocate this approach. In Spain, where resistance levels are higher than in most other countries in Western Europe, a task force has made recommendations to influence prescribing, but it is too early for any evaluation of the impact [188]. However, the peak of antibiotic usage in the community occurred between 1966 and 1976; usage fell between 1976 and 1988 and has remained at this lower level since then. If reducing community usage automatically resulted in falling resistance levels, Spain should have no need for this task force. In fact the great increase in penicillin-resistant pneumococci in Spain came since 1988, in the period of lower usage.

13.3.3   HOSPITAL EXPERIENCE AFTER CHANGES IN ANTIBIOTIC POLICY

Hospital-based studies are even harder to analyse than those from the community, as an increased emphasis on control of infection often accompanies antimicrobial restriction. Even when this is not formalised, the change to antimicrobial policy may increase awareness of infection and attention to hygiene.

This confounding variable was controlled in a recent study [241]. The authors studied a haematology unit where ceftazidime was the first-line therapy for febrile episodes in neutropenic patients and where there was a high incidence of infection and colonisation by glycopeptide-resistant enterococci. Ceftazidime (which has no activity against enterococci) was replaced by piperacillin/tazobactam (which has moderate activity) and strict hygienic precautions were enforced. The incidence of colonisation with vancomycin-resistant enterococci fell to a negligible level, but rose again when ceftazidime re-replaced piperacillin/tazobactam *with the hygienic precautions still in place*. It was concluded that the first-line antibacterial agent was the primary factor in determining whether or not enterococci caused super-infection.

A final study, and one of the most optimistic, is by Betts *et al* [242], who examined trends in aminoglycoside resistance at a university hospital after substitution of amikacin for gentamicin as the first-line aminoglycoside in empirical therapy. Rates of gentamicin resistance fell across a range of gram-negative species, including *Pseudomonas aeruginosa, Providencia* spp, *Proteus* spp and *Serratia* spp in the 4 years after the change was made (Figure 14). Allowing that multiple species were involved, it is clear that these observations did not simply reflect the displacement of a single epidemic strain. The authors noted virtually no emergence of amikacin resistance, but others who tried the same strategy were not so successful [16]. It should perhaps be added that, at the time of Betts' study (1984), most doctors in the UK perceived amikacin as the reserve aminoglycoside, only to be used against gentamicin-resistant organisms. Betts' approach was akin to that of those who now argue that we should use the most powerful antimicrobial agents first, so as to obtain the greatest benefit (this is rarely proposed in the UK, but is voiced in France and the USA).

In summary, the relationship between increasing use of antimicrobial agents and increasing resistance is clear beyond reasonable doubt, but the potential to reduce resistance by reducing use is much less certain and seems likely to vary with the particular combination of organism and antimicrobial agent. Success seems most likely where resistance entails a strain epidemic (as with *Salmonella typhimurium* DT 29) or a species epidemic (as with enterococci) and least likely where resistance genes have disseminated among strains or species.

Although reducing antimicrobial use may not reduce rates of resistance, it should reduce the rate at which new resistance accumulates, and this may be critical.

FIGURE 14   **GENTAMICIN RESISTANCE AFTER FORMULARY SUBSTITUTION BY AMIKACIN**
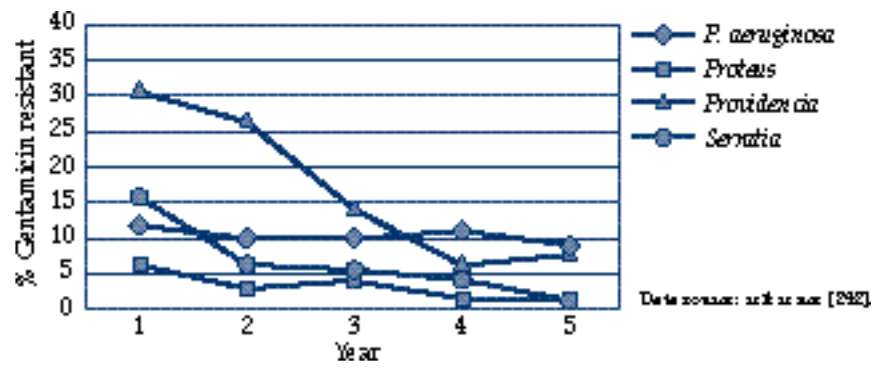
14 DEVELOPMENT OF NEW ANTIMICROBIAL AGENTS

KEY POINTS

Antimicrobial research is now more systematic and can screen vastly increased numbers of candidate compounds

New antimicrobial agents are under development, but success cannot be guaranteed

Development cost is high (£350 m) and patent life is brief (17 years)

Anti-infective drugs are not among the most profitable pharmaceuticals

Vaccines may be an answer to *Streptococcus pneumoniae*, but vaccines against other key pathogens are not in prospect

Despite much effort, little progress has been achieved in developing non-antimicrobial treatments of infection (eg based on immune stimulation)

The thrust of this report is focused on the conservation of present antimicrobial agents. However, it must be recognised that the way in which past resistance problems have been overcome (if only temporarily) has been by the development of new agents. It is also recognised that over recent years the pharmaceutical industry has developed vastly more efficient systems for seeking new antimicrobial agents. These strategies will, hopefully, yield new generations of antimicrobial agents by the end of the next decade.

14.1	DEVELOPMENT OF NEW ANTIMICROBIAL AGENTS

Development of a new antimicrobial agent costs c. £350 million, takes 7–10 years, and yields a product used for brief periods against targets prone to develop resistance. Its use may be restricted to delay resistance or to reduce costs. It is easy to comprehend why pharmaceutical companies may prefer to invest elsewhere and the number of Investigational New Drug permits for antimicrobial agents issued by the FDA in the USAhas fallen from 59 in 1993 to 12–22 in 1994–96. The surprise is that most major houses retain anti-infective programmes, not that others have left the field.

Many antibacterial agents have been launched in the past decade, but all are derivatives of old classes and, since resistance to the old class is (often) widespread, there is also a potential for swift multi-focal development of resistance to the new agent. No new *class* of antimicrobial agents has been licensed in the past 15 years .

14.1.1 NEW ANTIMICROBIAL AGENTS PRESENTLY UNDER ADVANCED DEVELOPMENT

Several compounds presently under development are promising, especially against MRSA and GRE (Table 23). The oxazolidonones and everninomycins are the first new classes of antimicrobial agents to be developed for 15–20 years. However, it should be stressed that the compounds listed in Table 23 are developmental drugs and there is no guarantee that they will be marketed. Specific concerns are:

i)   *Many developmental compounds meet toxicological problems and are not progressed.*
ii) *Although the many new quinolones have improved activity against* Streptococcus pneumoniae, *it is already apparent that resistance can develop.*
iii) *None of the new agents except clinafloxacin offers improved activity against gram-negative organisms.*

TABLE 23

NEW ANTIBACTERIAL AGENTS UNDER DEVELOPMENT 1998

COMPOUND	CLASS	COMPANY	ACTIVITY				
			MRSA	GRE	Pen^R Pneumococci	Multi-resistant gram-negative rods	M. *tuberculosis*
Oxazolidonones eg linelozid	Novel	Pharmacia Upjohn	+	+	+	−	+
Dalfopristin/ quinapristin (Synercid)	Virginiamycin	Rhone-Poulenc Rorer	+	+*	+	−	?
Everninomycin	Novel	Schering-Plough	+	+	+	−	?
LY333328	Glycopeptide	Lilly	+	+	+	−	−
Glycylcyclines	Tetracycline	Wyeth	+	+	+	±	?
Novel quinolones eg levafloxacin, trovofloxacin, grepafloxacin, clinafloxacin	Quinolones	Roussell Pfizer Glaxo Wellcome Parke Davis	+†	±†	+		±**?
Sanfetrinem, L345	Carbapenems	Glaxo, Merck	−	−	+	+**	?

*   *E. faecium* not *E. faecalis.*
**   No better than present agents, except clinafloxacin.
†   Experience suggests that resistance is likely to develop.

14.1.2   NEW STRATEGIES IN ANTIMICROBIAL DEVELOPMENT

Despite the recent dearth of new antimicrobial agents there are several promising factors for antimicrobial development, on a 10-year view

First, the new science of 'genomics' may yield new families of antibacterial agents. Genomics depends on sequencing the entire chromosomes of bacteria and identifying essential genes that are common to all, but which have no equivalent in man. The products of these genes can then be characterised and antibacterial agents tailored to attack them. Over 100 such genes have been identified and the approach is extremely promising.

Second, the methods of synthesising new candidate drugs have become vastly more efficient, through such advances as combinatorial chemistry, with the output per medicinal chemist rising from 30 compounds p.a. to over 10,000! Moreover, recombinant DNA methods allow genes (which may encode the synthesis of new natural antimicrobial agents) to be cloned from micro-organisms that cannot be grown in the laboratory. Other non-conventional antimicrobial sources are also being investigated, including for example, amphibian skin.

Thirdly, methods of screening antimicrobial activity have been vastly improved, with many pharmaceutical companies now able to test 20,000 compounds per day, compared with 200–300 a decade ago. Testing of up to 200,000 compounds per day may be feasible in the near future. This increased testing capacity is vital to balance the increased ability of medicinal chemists to make new compounds.

These strategies may yield whole new families of antimicrobial agents towards the

end of the next decade, but even if this optimism is justified there will be a window beforehand with resistance accumulating and a dearth of new antimicrobial agents. Furthermore, it is virtually certain that resistance will develop to new compounds and good prescribing habits are desirable to prolong their life once they do appear.

14.2   NEW VACCINES

Vaccination is one of the safest and most cost-effective ways of preventing disease. It enabled the eradication of smallpox and should also allow that of polio. Had this Report been written 10 years ago, resistance in *Haemophilus influenzae* causing meningitis would have commanded a major section, but the recent introduction of the Hib vaccine has virtually eliminated *Haemophilus influenzae* type b as a cause of childhood meningitis from the USA and much of northern Europe, including the UK.

Pneumococcal disease and tuberculosis are both major targets for vaccine development, along with malaria and HIV disease. Good progress is being achieved in the case of pneumococcal vaccines and the new formulations, unlike those presently available, are effective in children under 2 years of age [243]. However, providing protection against all 70 different subtypes (serotypes) of *Streptococcus pneumoniae* with a single vaccine is problematical. Vaccines presently available or under development protect against between 5 and 23 of the more prevalent types and it is feared that their use will select for other, hitherto rarer, types.

Progress against other key pathogens has been poorer. BCG remains in use as an anti-tuberculosis vaccine, although controlled trials give very variable estimates of its efficacy – from 0% to 80%! The nature of protective immunity to tuberculosis in man is not well understood and the development of better vaccines remains a major challenge. Likewise, development of vaccines against pathogenic *Neisseria* spp has met with only partial success (*Neisseria meningitidis*) or with failure (*Neisseria gonorrhoeae*). Research on anti-staphylococcal vaccines is at a very early stage, with no prospects for early development.

Gram-negative rods and enterococci are components of the healthy gut bacterial flora and vaccination, even if possible, might be harmful. Moreover, many different species are implicated as opportunist pathogens in patients who have severe underlying disease; effective vaccines against some species would only open an ecological niche for others.

14.1.3   NON-ANTIMICROBIAL AND ADJUNCTIVE THERAPIES FOR INFECTION

Many agents and strategies fall into this category, ranging from 'biological response modifiers' designed to boost the patient's defences, through to probiotics – harmless commensal bacteria used to competitively displace an undesirable bacterial flora. Both may be useful, but neither seems likely to replace antimicrobial agents on a wide scale.

Biological response modifiers are likely to be expensive and are likely to find their role, if at all, as adjuncts to antimicrobial agents in the treatment of serious infections. Several have reached clinical trials (tumour necrosis factor, anti-endotoxin antibodies, granulocyte monocyte colony stimulating factors), but so far each has yielded disappointing results.

Probiotics are most likely to find a role in chronic superficial infections such as

thrush and, perhaps, in the elimination of *Clostridium difficile* infection [244]; they will not provide a means of treating infections at what should be sterile sites, eg the bloodstream, upper urinary tract or lower respiratory tract.

Other suggestions include the use of bacteriophages (antibacterial viruses) [245] or exploitation of the antimicrobial properties of non-antimicrobial drugs. The use of phages was the topic of a recent *Horizon* television programme, which occasioned much public interest. However, the strategy presents problems: delivery of phage to the site of infection is difficult, resistance may arise and bacteriological diagnosis is needed to strain rather than species level [246] so that the correct phage can be used. Whilst some non-antimicrobial drugs have antimicrobial activity [247], it is difficult to see how they could become major replacements for established antimicrobial agents.

In summary, whilst research on unconventional approaches to the treatment of infectious disease deserves to be encouraged, it is unwise to anticipate swift results or broad applications.

15 PROMOTING GOOD PRACTICE

From the preceding sections of this report, it is clear that resistance is increasing – to many antimicrobial agents and in many species – and that in the worst cases we face the prospect of having no useful antimicrobial agents for some infections. Development of new antimicrobial agents is in progress, but will take time – moreover the efficacy of new compounds cannot yet be guaranteed. Careful use of antimicrobial agents, with prevention of cross-infection, can minimise the emergence and accumulation of resistance, but once resistance has accumulated it cannot readily or reliably be displaced.

The recommendations made in Section 2 of this Report are based on these premises. Their rationale is presented in these final sections.

PROMOTING BETTER PRESCRIBING

There are several ways in which improved prescribing can be encouraged

• evidence-based guidelines for prescribing (or not prescribing)

• computer-assisted prescribing to aid antimicrobial choice, or to help convince the physician and patient that no antimicrobial agent is needed and

• swifter microbiological diagnosis to minimise the use of unnecessary or unnecessarily broad therapy

BOX 13   **BETTER PRESCRIBING**

- Stop unnecessary use of antibiotics
  eg viral upper respiratory tract infection
- Shorten unnecessarily long courses
  eg cystitis; surgical prophylaxis
- Avoid inappropriate repeat prescriptions
  eg repeat courses without microbiological confirmation
- Avoid inappropriate broad-spectrum antibiotics
  eg ciprofloxacin for upper respiratory tract infection
- Further research into areas of possible inappropriate prescribing

16.1   **BETTER PRESCRIBING**

16.1.1   GUIDELINES FOR USE OF ANTIMICROBIAL AGENTS

The huge variation and incompleteness of current prescribing guidelines in many centres has already been emphasised (Table 21; Section 12.7). This is prone to lead to excessive and inappropriate use of antimicrobial agents. Where no guidelines exist, wholly inappropriate antibiotics are often used. In this context, it is notable that there are winter peaks in fluoroquinolone prescribing in the UK [248]. This seasonality implies use in respiratory tract infection, confirmed by analysis of prescribing data (IMS HEALTH Mediplus® Database UK PCD) and this use is not widely appropriate with present quinolones.

The development of national evidence-based guidelines, in conjunction with systematic reviews in key areas, will help clarify the current variation in the multiple sources of antimicrobial guidance (ie published papers, local guidance, the British National Formulary, the Dental Formulary and the Summaries of Product Characteristics (SPC) given in the APBI Compendium). Variation in authoritative advice is likely to lead to confusion and delay implementation of change [249]. Evidence-based antimicrobial guidelines are urgently needed, particularly for common conditions treated in the community. These should be produced under the auspices of the National Institute for Clinical Excellence (NICE).

Local guidelines should take their cue from these national guidelines to avoid re-invention of the wheel and should include, as minimum, information on the drug, its dosage and the route and duration of therapy. At a local level, Health Authorities should be encouraged to incorporate the guidelines in their Health Improvement Programmes, which are to be developed in conjunction with Primary Health Care/Local Health Care Groups.

Guidelines should be sufficiently flexible to accommodate regional and local differences in the prevalence of antimicrobial resistance, especially in hospitals. Such differences would be informed by an antimicrobial resistance surveillance programme (Section 17). It is not suggested that there should, for example, be a 'national standard regimen for UTI'; rather *that there should be a series of potential*

regimens, designed to optimise success and minimise the emergence of resistance, with the choice between these based on local circumstances.

The implementation of guidelines should be linked to an audit programme. This could be initiated and co-ordinated by NICE, but implemented at regional levels through postgraduate continuing education and clinical audit structures. Audit will reinforce and facilitate change through education and social interaction.

The guidelines should be incorporated into computer-aided decision-support systems (Section 16.1.2). This will make them accessible and easily shared with patients, so helping the prescriber to explain why a prescription may not be necessary.

It was not within the remit of the Sub-Group to draw up a long list of necessary guidelines and it is proposed that this topic should be co-ordinated by a National Steering Group (NSG), to be established to oversee the implementation of the recommendations in this Report. The NSG would work in liaison with the NICE and appropriate Health Authorities, primary care groups, Royal Colleges and national societies to review antimicrobial regimens, aiming to identify those that achieve clinical efficacy while minimising the emergence of resistance.

A problem is that, for many drugs, there is scanty evidence on the relationship between regimen (dosage and duration) and the risk of selection of resistance. For new antimicrobial agents, it is desirable that studies on these aspects become integral to licensing and post-marketing surveillance. Additionally, licensing authorities should consider whether an antimicrobial agent is likely to cause resistance to itself and other agents, as well as considering its efficacy and safety.

Whatever the limits on available data, some simple guidelines can be stated at this stage, based on discouraging well-known poor practice that uses antimicrobial agents unnecessarily or excessively. These include key advice included in our proposed CATNAP campaign (see Box 2).

16.1.2   COMPUTER-ASSISTED PRESCRIBING (or non-prescribing!)

Improved prescribing can be encouraged by computerised advisory systems. The prescriber enters clinical details into the computer together (or not) with the intended antimicrobial agent. The computer may then:

i)   *agree with the prescription*
ii)   *suggest an alternative antimicrobial agent that is more appropriate in view of the likely pathogen and local resistance patterns*
iii) *suggest issue of a post-dated prescription only to be filled if symptoms persist*
iv)   *suggest that no therapy is warranted*

Such systems have been developed, piloted and used extensively in some hospitals. One system in the USA[250,251] has been designed to 'enable clinicians to augment their clinical decision-making skills rather than to replace or control them' and 'to use locally-derived data with respect to resistance to guide the selection of drugs' [251].

To test the need for antimicrobial therapy and to guide the choice of drug and regimen, the computer uses:

i)   data on the patient's diagnosis and clinical status
ii)   microbiological results or, if therapy is empirical, epidemiological resistance data for likely pathogens
iii) information on drug cost

An 'Explain logic' option allows physicians to review the rationale for what is being suggested. If a physician prefers to use some other antimicrobial agent then he or she can over-ride the computer, which will still advise on dosage, duration and infusion rate, if relevant.

In one evaluation [251], the use of antimicrobial agents was reviewed before and after the system's application to a 12-bed shock/trauma intensive care unit. A total of 545 patients were treated during the intervention period compared with 1136 in the two preceding years. After adjusting for differences in the patient groups and for the fact that the system was often over-ridden for the most seriously ill patients (who received the longest and most complex antimicrobial regimens) it was concluded that computer-assisted prescribing achieved reductions ($p < 0.01$) in:

i)   orders for drugs to which patients were allergic
ii)   antimicrobial agent/susceptibility mismatches
iii) days of excessive drug dosage
iv)   adverse effects associated with antimicrobial agents
v)   cost of therapy and overall hospitalisation cost.

The authors concluded that 'The program has demonstrated such dramatic improvements in clinical and financial outcomes, as well as remarkable acceptance by physicians, that it has been requested and installed in additional in-patient and out-patient facilities in our integrated health care delivery system'.

Similar hospital systems, such as the computer-aided prescribing support described at the University of Birmingham [252], are under development in the UK. They require urgent wider development and evaluation as prescribing aids for the UK. They need to be able to respond to local differences in the prevalence of resistance; thus any national system would need to be adaptable to local conditions.

The potential for the use of such systems also exists in primary care, where there is likely to be less local variation in pathogen prevalence and resistance than in hospitals. Again the possible use of such systems deserves urgent investigation [253,254]. One such system *'PRODIGY'* is a knowledge-base that can be integrated with clinical management systems. Its aim is to support the GP in decision-making and to involve the patient. The user is led through a series of decision pathways to a recommended course of action. This contains advisory fields for physicians and informative fields for them to share with their patients, together with fields for storing records on the patients. The advisory fields could be used to highlight antimicrobial guidelines, locally modified as necessary in response to the local prevalence of resistance. The computer fields shared with the patient could be used to generate 'post-dated' or 'no antimicrobials needed' prescriptions, where appropriate, reinforcing the advice given by the physician.

The prescriptions recommended are derived from national guidelines being developed by the project. These are quality-assured by an expert panel including representatives from the Royal Colleges and the Royal Pharmaceutical Society of Great Britain. Antimicrobial agents are included in the guidelines according to

hierarchical criteria which include efficacy, adverse effects, compliance and cost.

Other similar systems are under development and need to be integrated with primary care clinical systems so that they are acceptable to GPs. They have great potential for improving prescribing of antimicrobial agents and their further development, introduction and evaluation should be encouraged.

16.1.3   IMPROVING EMPIRICAL THERAPY THROUGH SWIFTER DIAGNOSIS

In many cases empirical therapy is given when only a small subset of patients – the minority with bacterial infections – is likely to derive any benefit. It is estimated that 90% of patients with sore throats have viral infections and will not benefit from antibiotics, but that about 10% have *Streptococcus pyogenes* and risk late complications (notably rheumatic fever if rheumatogenic strains are prevalent), if they are *not* given antimicrobials (see Box 6). The problem is to identify this minority.

Simple pathogen detection tests can be introduced into GPs' surgeries and are valuable if they give an instant result and are sensitive and specific. Meier *et al* [255] found that an antigen-detection test for *Streptococcus pyogenes*, which gave immediate results with throat swabs, led to a reduction in the proportion of culture-negative patients who were given antibiotics from 53% to 32%. The savings on antibiotic costs offset the cost of the tests, irrespective of any long-term gain achieved by reducing antibiotic usage. On the other hand, a slide-culture technique for detection of *Streptococcus pyogenes*, which demanded overnight incubation, led to no improvement in antimicrobial usage. Treatment was initiated before the results were available in 84–90% of cases and was rarely (1–3%) altered or discontinued once results were available [256].

Urine dipsticks can be used in general practice to detect nitrites, which are products of bacterial nitrate metabolism [41]. If nitrites are found, infection is inferred and therapy started. This conclusion can be double-checked by a simple test for leucocyte esterase, which is an enzyme associated with pus cells, whose presence again indicates infection.

In the hospital setting, there is limited American evidence that physicians are more likely to change therapy if they receive susceptibility data early, before it is obvious whether or not the patient is responding to the empirical regimen. Data on this topic [257] are summarised in Table 24, showing results for isolates from 226 bacteraemic patients. Specimens from 110 patients were processed by a rapid, automated system (Vitek) which gave susceptibility and identification results in an average of 8.8 h, whereas specimens from 116 patients were processed by classical methods, giving results in an average of 48 h. Recommendations from the rapid system were less likely to be ignored than those from classical methods. The authors emphasised the potential for cost saving (estimated as US $158/patient at 1989 prices), but emphasis could also be placed on reduced morbidity and on switching to narrower-spectrum agents and those less likely to select resistance.

Rapid automated systems are minimally used in the UK, but account for about a third of susceptibility testing in the USA. Besides yielding swift results, they can also be advocated on the basis of standardisation. On the other hand, they are expensive to purchase or lease, have high overheads, may lead to laboratory de-skilling and need constant updating to ensure that they recognise new resistances [258].

Within the next 10–15 years faster and more precise techniques for pathogen

detection and analysis may become available based on 'Gene Chip' technology. DNA is released from clinical material taken directly from the patient and is hybridised with a miniaturised array of 2000+ gene probes, designed to detect likely pathogens and their resistance determinants. This should allow therapy to be tailored immediately to the specific pathogen, minimising selection for resistance. The limits are likely to be cost and that the method may miss rare or novel pathogens and resistances. It should be seen as an adjunct to, not an alternative to classical microbiology.

TABLE 24	EFFECTS OF RAPIDLY AVAILABLE DATA ON EMPIRICAL THERAPY IN BACTERAEMIA

| | NUMBER OF CASES RECOMMENDATION MADE (number ignored) | |
RECOMMENDATION	Rapid method (n=110)	Classical method (n=116)
Initiate therapy	10 (1)	0 (1*)
Stop antimicrobial agents	6 (2)	4 (8*)
Change to cheaper agents	38 (5)	21 (16)
Change to more effective agents	8 (1)	1 (1)

* The excesses in these groups presumably reflect instances where therapy was started or stopped *despite the lack* of any recommendation to do so (although the paper is unclear on this aspect).

16.1.4 WHAT IS THE BEST STRATEGY WHEN THERE IS ANTIMICROBIAL FAILURE

First, one must ask whether the failure was caused by re-growth of the original pathogen, re-infection or super-infection? If failure entailed the survival of the original pathogen, was it resistant initially, did it develop resistance or did the antimicrobial agent fail to reach the infection site? Thought is required, not 'spiralling empiricism'.

Therapy sometimes fails because impossible tasks are demanded of antimicrobial agents. Abscesses need to be drained, necrotic tissue demands debridement, bacterially colonised lines and catheters need to be removed and replaced; antimicrobial agents cannot be expected to cure infections associated with these conditions. In many instances, infected prosthetic joints and valves also need to be removed and replaced, although the gain must be balanced against the risk of further surgery. Protracted antimicrobial therapy for conditions where surgery is advisable is likely to select further resistance. Thus, the first isolate of a vancomycin-intermediate *Staphylococcus aureus* was from an abscess in a child who had received vancomycin for over 1 month [48]. The infection was ultimately resolved by drainage, together with administration of arbekacin – an experimental aminoglycoside. Had drainage been undertaken earlier the evil might have been avoided.

Where therapy has failed without a focus of infection demanding drainage or removal, microbiological testing is mandatory. The results should guide the choice of the replacement drug, with preference given to agents that exert the least selection pressure for resistance on the normal bacterial flora.

The greatest problem arises when the patient's clinical condition continues to demand therapy but no pathogen is isolated. This applies in up to 70% of febrile episodes in neutropenic patients [259]. Further, the presence of an antimicrobial agent may preclude recovery of the pathogen whilst failing to clear the infection. In

these cases, therapy must be replaced or supplemented without laboratory support. The replacement antimicrobial agent should have the minimum possible cross-resistance with the first agent. In this context: (i) quinolone resistance is genetically independent of that to other antibacterial agents and (ii) resistance to carbapenems in gram-negative bacteria is largely independent of that to cephalosporins and penicillins [260]. The logic of avoiding switches between antibacterial agents with related resistances can also be followed in primary care practice. Thus, in urinary tract infection, resistances to quinolones, nitrofurantoin and fosfomycin are independent of each other and of resistance to ß-lactams and trimethoprim, whereas single plasmids often determine resistance *both* to ß-lactams and to trimethoprim. However, one caveat must be stated: evolution can change any recommendation!

In a few instances it is appropriate to *add* drugs to an empirical regimen, rather than to substitute. The main example is planned progressive therapy in febrile neutropenic patients. Here the EORTC (European Organisation for the Research and Treatment of Cancer) recommended initial regimens are ceftazidime/aminoglycoside or piperacillin-tazobactam/aminoglycoside or meropenem [259], with the choice between these regimens based on local resistance patterns. If the fever has not resolved within 48 h, with no pathogen isolated, the regimen is supplemented with a glycopeptide, as methicillin-resistant coagulase-negative staphylococci are the likeliest pathogens to have withstood the initial regimen. If the fever still does not respond, fungal infection is suspected and amphotericin is added. More generally, the practice of adding further antibacterial agents, rather than substituting, is to be discouraged. It remains common to see patients who are receiving bizarre mixtures of antibacterial agents, usually because the initial therapy was not stopped when a further agent was added. At best these mixtures are expensive and wasteful, at worst, the components may antagonise each other's activity.

16.1.5   ROLE OF THE MEDICAL MICROBIOLOGIST

All major acute hospitals in the UK are served by a department of medical microbiology, under the direction of a medically qualified consultant microbiologist. Most medical microbiologists have close links with their hospital and GP colleagues and collect information on the susceptibility patterns of their local bacterial isolates. Many of these departments provide prescribing information based upon these local patterns for use in hospitals and general practice.

Susceptibility patterns to many pathogens, particularly those in the respiratory tract, can vary considerably over short distances. Therefore, it is important to utilise the services of the local laboratory fully to make prescribing choices as rational as possible.

In the battle against antibacterial resistance, the local medical microbiology department can usually offer advice on infection control matters. As GPs undertake increasing numbers of procedures in their surgeries, it is especially important to ensure that responsible and thorough infection control advice is provided – again the consultant medical microbiologist should be the first port of call for such information.

The diagnostic facilities of the local laboratory can assist in the rational choice of antimicrobial agents by providing advice as to the timing and type of specimens to be sent to the laboratory. Some laboratories have guidelines as to whether, for example, sputum should be examined from all patients who have a respiratory tract infection, or only those patients in whom previous therapy has failed.

It is important that hospital doctors and GPs form firm links with their medical microbiology colleagues in the battle against antimicrobial resistance, with the aim of developing optimal prescribing patterns.

16.1.6   IMPROVING MEDICAL EDUCATION

The success of all these initiatives and advice depends on education. At present education on antimicrobial agents and resistance is often included in the early pre-clinical years of medical and dental training and is divorced from clinical situations where students are exposed to prescribing decisions. Antimicrobial prescribing is learnt later, once the students have started clinical training and often from those who learnt their own prescribing years earlier. As a result of this displacement, these topics are prone to become divorced from one another.

The pressures on medical microbiologists and the limited number of clinical infectious disease physicians means that there is a paucity of experts available to teach antimicrobial prescribing in the context of clinical medicine and microbiology. This is less than ideal. Trusts should ensure that their junior medical staff receive dedicated teach-ins on antimicrobial prescribing, since these are the doctors who most commonly initiate prescribing.

The exposure of clinical medical and dental students, pre-registration and senior house officers and postgraduates in all specialities to the issues of prescribing antimicrobial agents and the threat posed by antimicrobial resistance is critical to the attempt to encourage more cautious prescribing.

16.2   PROMOTING CONSERVATION OF ANTIMICROBIAL AGENTS

16.2.1   ROLE OF HEALTH CARE PROFESSIONALS OTHER THAN MEDICAL PRESCRIBERS

Although medical practitioners are responsible for most antimicrobial prescribing, other professionals also have a role: *dentists* are prescribers, albeit for only a fraction of total antimicrobial agents used, *nurses* influence whether antimicrobial agents are given by a doctor and *pharmacists* co-determine which antimicrobial agents are stocked and used by hospitals.

Finally, ALL staff in hospitals and community care facilities have a role in maintaining cleanliness and hygiene, which impact hugely on the transmission of infection and on the need for antimicrobial chemotherapy.

16.2.2   THE ROLE OF NURSES

Although clinicians have the remit to prescribe antimicrobial agents, it is highly desirable that nurses are familiar with prescribing protocols and with inappropriate use so that they can alert junior doctors, for example, when antimicrobial agents are being prescribed for excessively long periods.

Nurses also have a major role (both in hospitals and in the community) in helping patients to understand the nature of their illness and the actions and side-effects of prescribed medications. Consequently, they are in an excellent position to maximise

concordance and to provide and support educational material. They may be able to identify individuals and families in whom concordance is likely to be a problem and where single-dose therapy is desirable, if available.

Most of all, nurses – especially infection control nurses – have a key role in the prevention of infection, especially in hospitals. They should educate others in hand-washing, safe disposal of microbially contaminated material, essential use of disinfection and procedures to prevent cross-infection. Infection control policies need rigorous audit of effectiveness.

There is a critical role for nurses in the improvement of infection control policies in nursing homes, especially with the increased prevalence of MRSA in these establishments.

The successful implementation of any policy aimed at controlling the use of antimicrobial agents will depend upon surveillance of the resistance of samples from patients. Collection of samples is often undertaken by nurses; understanding this role is important in nurse training.

16.2.3   THE ROLE OF PHARMACISTS

Community pharmacists are frequently the first port of call for patients and also the point of contact when a prescription is collected. The role of pharmacists within the community, in providing services to nursing homes and monitoring their use of pharmaceuticals, is developing. These are areas where pharmacists could influence change in the prescribing of antimicrobial agents and help educate the public about concordance.

Hospital pharmacists also have an important role in improving antimicrobial prescribing, being involved in a number of key areas. They are well qualified to give advice to prescribers on changes of agent as well as suitable routes and durations of therapy. They may be able to help in the enforcement of prescribing policies.

Hospital pharmacists are involved in the audit of prescribing and therefore have a key role in the checking of adherence to antimicrobial prescribing guidelines. Furthermore, pharmacists commonly have input into the education of junior hospital doctors with regard to prescribing.

16.2.4   ALL HEALTH CARE STAFF IN HOSPITALS AND CARE FACILITIES

There is considerable (albeit anecdotal) evidence that alterations in cleaning contracts and reduced resources have had a detrimental effect upon the cleanliness of hospitals compared with 10 or 20 years ago, and that, under pressure of work, simple precautions such as hand-washing between patients are omitted.

Education on the importance of hygiene is essential for all health care staff.

In community long-term care facilities, there are often few if any precautions to reduce the transmission of infection, yet it is apparent (Section 12.10.3) that these establishments often represent reservoirs of patients colonised or infected with multi-resistant bacteria, especially MRSA. The consequence of this poor hygiene is increased use of antibiotics, together with its corollary – increased resistance.

The issues of hospital-acquired infection were addressed in the Cooke Report [1]; those of community care facilities, whilst apparent, have been less systematically

investigated. There is urgent need for guidance, similar in design to the Cooke Report, on infection control in the community.

16.2.5   THE ROLE OF VETERINARY SURGEONS AND AGRICULTURAL USERS

The use of antimicrobial agents in animals is significant in the selection of resistance, both in zoonotic pathogens and in those gut commensals that can act as opportunists or as vectors of plasmid-borne resistance. Veterinary surgeons, like physicians and human health care professionals, have a responsibility to use antimicrobial agents prudently. We recommend that the use of antimicrobial agents in veterinary practice should be guided by the same principles as in human prescribing, ie antimicrobial agents should be used only where their use is likely to yield a specific health benefit. Good husbandry should be encouraged to minimise the need for prophylactic antibiotics. Where prophylactic use is considered it should be guided by Hazard Assessment Critical Control Point (HACCP) principles (see Section 12.12).

A clear distinction must be drawn between therapeutic and prophylactic use of antimicrobial agents in animals, which is supervised by veterinary surgeons, and the administration of growth promoters which is not under veterinary supervision. This latter practice risks undermining new human antimicrobial agents as well as established agents (see Section 12.12). We recommend that alternative means of husbandry should be followed allowing the use of growth promoters to be discontinued.

16.3   PUBLIC EXPECTATIONS AND ATTITUDES TO ANTIMICROBIAL AGENTS

Over-prescribing of antibiotics partly reflects public expectation (see Section 12.10). If campaigns to reduce prescribing are aimed only at health care professionals, then these professionals will be left facing dissatisfied patients or carers, not all of whom take refusal kindly. We propose a campaign giving National Advice to the Public (NAP), to be run concurrently with the Campaign on Antibiotic Treatment (CAT) to reduce and rationalise prescribing in primary care. As most inappropriate use of antibiotics is for upper respiratory tract infection in the community, this usage should be targeted, with key messages that:

i)   *Patients should not expect antibiotics for trivial infections, especially of the upper respiratory tract.*
ii)   *GPs may give post-dated prescriptions when the need for an antimicrobial agent is doubtful.*
iii)   *Antibiotics are magic bullets – invaluable – but not to be taken lightly.*
iv)   *Taking antibiotics unnecessarily does you no good and damages them for everyone else.*
v)   *It makes sense to cherish your bacterial flora.*

Nevertheless it must be emphasised that swift antimicrobial therapy is essential for serious infections, eg meningitis.

Various ways of communicating these messages could be envisaged, from simple slogan-based advertising:

"Antibiotics cure serious diseases – not colds, coughs and wheezes.........
Save them for when it's important "

through billboard advertising and bus-side advertising, as was done in the West Midlands [248] (Figure 15) and on to patient information leaflets such as those produced in America by the Alliance for the Prudent Use of Antibiotics (Figure 16).

ADVERTISING TO DISCOURAGE ANTIBIOTIC USE

Reproduced with kind permission of Prof. S Chapman, Dept of Medicines Management, University of Keele.

Key messages on antimicrobial conservation should be communicated in schools, with information on antibiotics included in health education, perhaps as part of the National Curriculum. Children should be taught the difference between bacteria (which are killed by antibiotics) and viruses (which are not). The failure of many adults – and the press – to make this distinction accurately is a major obstacle to public understanding. Those responsible for designing school curricula should be encouraged to include antimicrobial resistance as an eloquent demonstration of evolution in action – and of evolution with very direct consequences for mankind.

PATIENT INFORMATION LEAFLET

Reproduced with kind permission of the Alliance for the Prudent Use of Antibiotics, Boston, USA.

CHERISHING YOUR FLORA – THE BENEFICIAL NATURE OF BACTERIA

The normal human microflora comprises more bacteria than there have ever been people upon the planet, with over 400 different species. The microflora has a role in the metabolism of nutrients, vitamins, drugs, endogenous hormones and carcinogens. This is poorly understood, but probably largely beneficial [261].

The microflora is probably protective against invasion by pathogens, notably *Clostridium difficile.* Infection by this organism can cause antibiotic-associated diarrhoea, and at worst, pseudomembranous colitis. *Clostridium difficile* can become established in the gut only when the normal bacterial flora has been disrupted by antibiotics. Certain bacteria, such as *Lactobacillus acidophilus*, appear to be especially beneficial in the gastrointestinal tract and interfere with establishment of pathogens [262]. **These aspects should be brought into the public domain and should be emphasised to medical students.**

Antimicrobial agents have harmful effects upon the normal and beneficial microflora, as well as upon pathogens. There is increasing evidence that maintenance of the normal microflora of the gut is important, and that restoration of the microflora may be beneficial in some chronic conditions [263,264].

The role of the normal resident microflora is now beginning to be understood and with understanding comes a realisation that we should be 'cherishing our normal bacterial microflora'.

SURVEILLANCE OF RESISTANCE

Surveillance needed to monitor trends

Surveillance needed to test effects of interventions

Programme is being assembled by PHLS and BSAC

Multi-faceted, with compilation of routine data and detailed prospective studies, each cross-validating the other

Comprehensive surveillance is required to measure the public health impact of antimicrobial resistance and of interventions (including those proposed in this Report) to minimise antimicrobial usage. At present, surveillance of resistance in the UK is limited, and is conducted largely by *ad hoc* studies by the PHLS, NHS laboratories and universities, often sponsored by the pharmaceutical industry. Sample sizes are often small and the studies are beset by sampling errors, because:

i) *specimens from unresponsive infections, possibly caused by resistant bacteria, are more likely to be sent for microbiological testing*
ii) *many studies are run from tertiary centres, whose resistance problems may exceed those of other establishments*
iii) *antimicrobial susceptibility testing – as performed in routine laboratories – is not standardised in the UK*

A more systematic approach based upon improved denominators is urgently needed. The PHLS, in liaison with the British Society for Antimicrobial Chemotherapy (BSAC) and other interested parties, is developing a multi-faceted national surveillance scheme. Its key components are outlined below. It is critical that this receives support both financially and in terms of encouragement for laboratories to participate.

17.1 ALERT ORGANISM SURVEILLANCE (EXCEPTION REPORTING)

Alert organism surveillance (exception reporting) involves detection of organisms with significant new features, such as vancomycin resistance in *Staphylococcus aureus*. Such organisms are important as potential harbingers of doom, but their importance is low in immediate public health terms, with perhaps only a single patient infected. Although not completely formalised, a system for exception reporting is in place, insofar as such organisms find their way to reference or academic laboratories for investigation.

17.2 REFERENCE LABORATORY MONITORING

At the next level, monitoring of organisms sent to reference laboratories also has its place. The organisms received represent those perceived by the sending laboratory as important or 'difficult'.

There are often no standardised criteria for selection. From the perspective of the source laboratory, such organisms are not submitted for surveillance purposes, but for confirmation of identity and resistance. The PHLS and academia have long records of performing elegant microbiology to characterise such organisms and elucidate mechanisms of resistance. In public health terms, however, such monitoring is beset by sampling problems and by the lack of a denominator.

17.3 SENTINEL LABORATORY MONITORING

Sentinel laboratory monitoring offers an answer to some of these problems, with prospective collection of selected organisms for testing by standard methodology.

This approach offers a high level of laboratory control, but the absence of a denominator population means that the results do not fully measure a public health problem. The number of isolates that can be tested centrally is, of necessity, small.

Linked to other sources of data, however, sentinel laboratory monitoring can make a major contribution. No such system is currently in place in the UK, but one will be incorporated in the new programme.

17.4 SPECIAL SURVEYS

Special surveys provide a useful means of clarifying details about particular organisms. The best have a defined population denominator, a clinical case definition rather than a laboratory one and microbiological standardisation. The best example in the UK is mycobacterial surveillance. Data collection is relatively easy here as virtually all susceptibility testing is at reference laboratories.

In summary, special surveys are a good tool, particularly when the approach is based on prospective selection with a clinical case definition in a defined population. However, special surveys cannot be performed for every organism and the costs are considerable.

17.5 SURVEILLANCE BASED ON ROUTINE SUSCEPTIBILITY TESTING DATA

Compilation of routine susceptibility testing data offers another opportunity and, as these data do have a population denominator, measurement of the public health impact is possible. Such data are collected via the PHLS CoSurv System. However, antimicrobial susceptibility data were not part of the original core specification of CoSurv and, except for blood and CSF isolates, the data are inconsistently entered and extremely difficult to extract for analysis. Moreover, there remains the problem of non-standard antimicrobial susceptibility testing methodology.

Other routine data, besides those for blood and CSF isolates, represent a huge untapped source of inexpensive, accessible results, which could be analysed at local, regional and national level to give a measure of the public health impact of antimicrobial resistance. The system envisaged – not presently in place – is thus one fed by regular downloads from laboratory computers of routine susceptibility data on a wide range of organisms and specimen types. The aim would be to encompass the whole; an essential facet would be linking the data to population denominators. Although this is a new area of work, the burden on individual laboratories would be relatively low – running a standard computer report at regular intervals (eg once a month). Electronic downloading of the data direct from microbiology computer systems is the ideal to aim for and has been attained by at least one commercial system covering 150 laboratories monitoring resistance in the USA[TSM Database: http://www.thetsn.com].

17.6 PRESCRIBING DATA

Those methods that enable linkage to population data provide the opportunity to cross-relate with prescribing data. These data are available in great detail for primary care (GP) and are linked to population data but there are no antimicrobial resistance data against which to analyse them. For example, there is a 30% variation in antimicrobial costs between the lowest and highest prescribing districts in Trent, yet

the public health impact of this difference has not been measured. The new programme will link resistance prevalences with prescribing data.

17.7 INTERPLAY OF SURVEILLANCE PROGRAMME COMPONENTS

Each of the above surveillance components will play a valuable part in the overall programme, but no single part can provide all the answers. The alert organisms and reference laboratory components will identify unusual resistance deserving priority work, but will provide minimal denominator data. The sentinel laboratory and special surveys will provide high quality microbiology and quantitative measurement of levels of resistance, but with small sample sizes. Routine data will provide mass information, suitable for relation to prescribing and population denominators, but will be based on routine tests, which are of variable quality and depend on sampling decisions by doctors.

Collectively, however, these component activities will cross-validate each other. The sentinel laboratory and special studies will test the quality of the routine data, while the appearance of trends (or unexpected results) in the routine data will inform the choice of organisms requiring enhanced surveillance by sentinel and *ad hoc* approaches. Where both approaches identify the same trend, then the evidence for the trend is greatly strengthened; where the routine and enhanced surveillance data sets conflict, the reasons will be investigated, perhaps leading to interventions in the methods of susceptibility testing.

17.8 ADDITIONAL NEEDS FOR EFFECTIVE SURVEILLANCE OF RESISTANCE

Surveillance is only as good as the data it collects. Several major concerns can be raised about the routine susceptibility testing data available. First, routine susceptibility tests in the UK are notorious for their lack of standardisation and are carried out mostly by a method (Stokes plates) that has been superseded elsewhere in the world [265]. The British Society for Antimicrobial Chemotherapy has a major initiative to supplant this method with a better standardised disk test. This will be adopted by the PHLS as a Standard Operating Procedure, but its uptake by other laboratories may be slower. Other problems are less tractable. In particular: (i) most laboratories test relatively few antimicrobial agents against most isolates and not all test the same compounds, thus the data collected are likely to be patchy; (ii) some 'second-line' antimicrobial agents are tested only against isolates resistant to more widely used agents; and (iii) many isolates, particularly of gram-negative bacilli, are only partly identified, meaning that major resistance developments in infrequent species are likely to be missed. The only answer to this problem is a major investment to improve the quality of routine medical microbiology in all microbiology laboratories. Without this, surveillance based on routine data risks being a case of 'rubbish in, rubbish out'.

17.9 COMMUNICATION OF LOCAL SURVEILLANCE RESULTS

Data on *local* rates of pathogen prevalence and resistance are often poorly disseminated from the laboratory to physicians, both within hospitals and in the community, yet this information should be fundamental to the choice of empirical therapy. Better communication of these data is essential. It should be emphasised that local data are needed and that dissemination must inevitably be handled locally. This is not part of the national surveillance discussed earlier.

In the USA, ward-based physicians often have simple cards detailing rates of resistance in key pathogens at their hospital. These are rarely seen in the UK, but could readily be provided. Ultimately the computer-assisted prescribing support systems described earlier (Section 16.1.2) should help to overcome this problem.

18   RESEARCH ON RESISTANCE AND ON NEW ANTIMICROBIAL AGENTS

KEY POINTS

Academic research on resistance has a low profile

The importance of academic medical microbiology needs upgrading

Key areas for public sector research are identified

Industrial research on new antibiotics needs encouragement

Whilst the problem of resistance is clear, there are many aspects on which our understanding is limited. Consequently, there is much scope for useful research in the public sector, whether at PHLS laboratories, NHS hospitals or universities.

The development of new antimicrobial agents is costly and is the domain of private industry, but needs encouragement.

18.1   PUBLIC SECTOR RESEARCH ON ANTIMICROBIAL RESISTANCE

The profile of research on the epidemiology and basis of resistance needs to be raised. In recent years these topics have been given a low priority by the more prestigious funders of biomedical research. Some sponsorship of research in the field has been provided by highly regarded charities (eg the Cystic Fibrosis Trust) and by hospital trustees but, more generally, funding has been from the pharmaceutical industry. However good the projects, sponsorship from this latter source has been viewed as a 'milch-cow' by the universities, although it has had a low status rating in research assessment exercises.

The adverse consequences of this low status are manifold and the problem has been exacerbated by the recent retirement of several leading UK figures in the field and, particularly in London, by hospital and university mergers. Specifically:

i) *At least three London teaching hospital microbiology departments with long records of research on resistance are being, or are under serious threat of being, down-sized.*
ii) *Antimicrobial research in universities is, in general, receiving little new commitment and investment (Leeds is an exception).*
iii) *There is a shortage of good PhD students wishing to enter the field and consequently a shortage of good post-doctoral scientists emerging.*

This shortage of good post-doctoral scientists is among the reasons cited by SmithKline Beecham for moving their antimicrobial research programme from the UK to the USA. Ten years ago, four UK pharmaceutical companies (Beecham, Glaxo, Wellcome and Zeneca) had major anti-infective research programmes in the UK – as did one American company (Pfizer). Now only Pfizer and Zeneca retain these programmes; the others have merged, or have moved their programmes overseas.

Unless reversed, this degrading of expertise impacts on the skills needed both to develop new antimicrobial agents and to understand and contain resistance.

It is suggested that the items in Box 14 are key aspects meriting further study.

BOX 14

ASPECTS MERITING FURTHER RESEARCH

- Factors driving resistance
- Mathematical modelling of resistance
- Geographical information systems
- Basic molecular research on mechanisms of resistance
- Links between prescribing and resistance at individual and population levels
- Beliefs concerning antibiotic use and their influence on demand and concordance
- Factors leading to inappropriate prescribing
- The role of social change – particularly day-care of the elderly and children – and related infection control problems
- Development and assessment of computerised decision-support systems in hospitals
- Investment versus restriction in antimicrobial use

Developing a new antimicrobial agent is expensive (£350 million). The compound then 'enjoys' a patent life of 17–20 years, depending on the country. Nearly half of this has already expired before the compound is launched. On these economics, companies will not prioritise investment in antimicrobial agents if their use is to be greatly restricted. If restriction leads to a slowing (but not a reversal) of the accumulation of resistance, but also stifles innovation, the position will continue to deteriorate.

It is important that reduced prescribing, arising from this Report and other initiatives, does not stifle any renaissance in antimicrobial development. We recommend that consideration is given by the appropriate bodies to finding ways – through pricing or other mechanisms – to ensure that antimicrobial development remains a worthwhile financial risk for the industry.

One possible way forward, balancing the need for continued innovation with that of drug conservation, lies in a trade-off between extended patent life and increased restriction. Another way to encourage antimicrobial development might be to streamline the licensing process as, for example, has already been done with anti-HIV drugs. However, these would need agreement across the EU, which now controls UK drug licensing and patent law.

CHANGING PRACTICE

Change is always painful, even from worse to better (Oscar Wilde)

Although the terms of reference of the Sub-Group were to concentrate on changing professional activities in order to reduce antimicrobial resistance (Box 1), research on 'change management' concludes that this cannot be undertaken in isolation. The overall culture and organisation in which professionals work has to be addressed at local and national levels. This includes modifying patients' expectations.

There have been many attempts to identify effective strategies for bringing about change in professional behaviour, ranging from systematic reviews summing the evidence of clinical trials, to qualitative techniques in which practitioners are directly asked about what makes them change their practice [266, 267].

These studies have assessed a range of individual methodologies, alone or in combination:

i)   *continuing medical education*
ii) *guidelines*
iii) *computerised decision supports*
iv) *one-to-one transmission of information*
v)   *activities of opinion leaders*
vi) *participation of clinicians in trials*
vii) *provision of research-based information to patients*
viii) *clinical audit and feedback*
ix) *organisational policy and legislation*

No single method is superior but some general lessons have emerged. Change needs to be carefully planned. All essential protagonists need to be identified, as well as the associated barriers. Specifically designed interventions need to be implemented for each obstacle. The whole process must be co-ordinated and progress evaluated.

Educational, epidemiological and marketing approaches appear particularly effective at the dissemination stage; marketing and social interaction approaches at the adoption phase; behavioural and organisational approaches at the implementation phase; and organisational and coercive approaches to maintain the desired performance. A single strategy is often inadequate and a combination is needed to achieve a lasting effect.

Individuals work in a local, national and increasingly, international environment. Unless specific changes are in sympathy with the prevailing culture(s), implementation is difficult. This is particularly important in a global problem such as antimicrobial resistance, which crosses many disciplines. If individuals are to respond they will need to be reassured that the need to change is being applied equally to all those involved and that there is a commitment from Government and policy-makers.

IMPACT OF GUIDELINE IMPLEMENTATION ON THE PROCESS AND OUTCOME OF CARE

Promulgation and application of guidelines are key recommendations of this Report and it is important to consider how effectively they can be introduced and what they can achieve. Two systematic reviews [266, 268] of the effectiveness of a wide variety of interventions to implement recommendations for changing clinical practice in different areas of medicine concluded that there is very strong evidence that practice guidelines can improve both process and care. In one of these [268], 91 evaluations were considered with 81 showing improvements in process and 12 (out of 17) improvements in patient outcomes.

Practice guidelines are more likely to be effective if locally relevant and actively implemented with end-users. They should be targeted to the clinical environment at the patient–clinician interface where decisions are made. Grol [269] points out that evidence-based medicine should be complemented by evidence-based implementation and that the model for implementing change should consist of five steps:

i)   development of a change proposal
ii)   identification of obstacles to change
iii) linking interventions to obstacles
iv)   development of an implementation plan
v)   conduct of plan and evaluation of progress

There is cumulative evidence from several studies [224, 242, 250, 270, 271] that antibiotic prescribing policies can change clinical practice, although these studies may focus on factors such as drug costs rather than resistance levels [250, 251, 272–274]. Alterations in prescribing practice have also been reported in community settings in Finland [19] and Iceland [239]. Education of GPs may be important [273, 275], but is not the only factor [159–161, 276].

In primary care a second level of behavioural change is necessary: the patient must also be educated not to expect antibiotics for minor infections. There is considerable evidence from the literature [160, 163, 164, 277] that such over-prescribing for self-limiting conditions will increase belief in antibiotics, but the review has found only one good study (by the same group) that demonstrates that patient education can reduce the demand for service [155].

CREATING AN ENVIRONMENT FOR CHANGE

In making recommendations aimed at influencing doctors' prescribing – principally the national Campaign on Antibiotic Treatment (CAT) in primary care – we acknowledge the importance of patients' expectations in the decision-making process. Therefore there should be a concurrent and co-ordinated programme to modify patients' expectations through public education; there should be National Advice to the Public (NAP). This will make it easier for GPs to adhere to prescribing recommendations.

This approach will need to be co-ordinated at a national level, hence the recommendation for a steering group charged with ensuring the implementation and evaluation of a nation-wide strategy. Monitoring of national progress could be

through existing performance management systems, which extend down to Regional and Health Authority levels.

Computer systems may improve access to the guidelines and hence facilitate their implementation. If the computer systems can be made relevant to both prescriber and patient this will assist in the consultation and help the prescriber to explain why a prescription may not be necessary.

To be fully effective the guidelines will need to be up-to-date and locally relevant, otherwise they risk losing credibility. Therefore, the guidelines need underpinning with local antimicrobial sensitivity data. These in turn should feed into regional and national surveillance databases. Thus, the national surveillance strategy for denominator-based resistance surveillance currently under development (Section 17) is critical to improving antimicrobial prescribing practices.

The results and analyses from national and local surveillance will allow the closure of the audit feedback loop and adaptation and revision of guidelines, as well as providing outcome data for studies to identify the drivers of resistance and the effectiveness of interventions to improve antimicrobial prescribing.

IN CONCLUSION

Antimicrobial prescribing is an activity with roots in many cultures, clinical and lay. It is only through addressing all of those involved that we are likely to find

The Path of Least Resistance

20 INDEPENDENT REVIEW OF THE LITERATURE

20.1 INTRODUCTION

As part of the process of preparing our Report, the Sub-Group on Antimicrobial Resistance commissioned an independent review of the literature to determine the nature and quality of the evidence that changing prescribing patterns could result in reduction or limitation of the spread of antimicrobial resistance.

20.2 AIMS

To assess the evidence that inappropriate use of antibiotics leads to increased levels of antimicrobial resistance.

To assess the quality of evidence that antimicrobial resistance levels can effectively be reduced or reversed.

To examine the evidence that effective implementation of changes in prescribing practices will result in reduction of antimicrobial resistance levels.

To provide independent confirmation, or otherwise, that the conclusions reached in the main report are justified.

20.3 METHODOLOGY

MEDLINE searches were carried out to identify relevant studies published in the last 10 years. A search of the BIDS database was also employed. Searches used both appropriate keywords and MeSH terms such as 'Drug resistance, microbial' and 'Prescriptions, drug'. Additional papers were identified from the reference lists of these papers, grey literature including conference reports, and the work of key authors. The main focus was Western Europe and North American studies.

The quality of the research was critically appraised and graded using a slightly modified version of the criteria developed in the NHS Centre for Reviews and Dissemination, University of York, in conjunction with the Cochrane Collaboration.

The grading was that of the independent reviewers.

Grade I (Strong evidence)
Randomised controlled trial or review of randomised controlled trials

IA: Calculation of sample size and accurate and standard definition of outcome variables
IB: Accurate and standard definition of outcome variables
IC: Neither of the above

Grade II (Fairly strong evidence)
Prospective study with a comparison group, (non-randomised) controlled trial or good observational study

IIA: Calculation of sample size and accurate, standard definition of outcome variables and adjustment for the effects of important confounding variables
IIB: One of the above
IIC: None of the above

Grade III (Weak evidence)
Retrospective study

IIIA: Comparison group, calculation of sample size and accurate and standard definition of outcome variables
IIIB: Two of the above criteria
IIIC: None of the above

Grade IV (Weak evidence)
Cross-sectional study

In addition several papers were reviewed which involved *in-vitro* experimental techniques, using bacterial cultures. There is no standard grading for the quality of such evidence. It was, therefore, divided into three grades (using Arabic numbers)

1. Good *in-vitro* evidence
Standardised prospective experimental procedures with good controls and clearly defined conditions

2. Fairly good *in-vitro* evidence
Good controls and clearly defined conditions in retrospective or non-standard procedures

3. Weak *in-vitro* evidence
Poorly controlled or defined experimental conditions.

20.4   SEARCH RESULTS

The basic MEDLINE search using the terms 'Drug resistance, microbial' and 'Prescriptions, drug' yielded 65 references over the last 10 years. However, eight of these were in a variety of languages other than English (Scandinavian or other European languages) and few had abstracts available in English. There was a preponderance of papers in journals which were not readily available.

Other key words were tried: 'Eradication' yielded references almost exclusively on *Helicobacter pylori.* 'Reduction' brought up many general references on infection control, while 'reversal' generated mainly articles on leprosy, HIV and several *in-vitro* molecular experiments, including the identification of resistance mechanisms and use of inhibitors. The limitations of MEDLINE were revealed by the failure to include the work of the Finnish Study Group for Antimicrobial Resistance (FIRE) until both 'Finland' and 'Erythromycin' were used as search terms.

A search of the BIDS database was less specific, but did yield about 12 relevant papers (out of over 200) including an editorial comment on the Finnish results.

In general the quality of the evidence was not high. No good randomised controlled trials were identified and few controlled prospective studies. This is not surprising as randomised controlled trials are not feasible in this field. Research designs normally regarded as of relatively poor quality for evaluation of clinical interventions may be the best available in this case. Such findings have been noted before in other areas of service delivery. Many papers were non-systematic reviews, conference reports and editorial comments rather than original studies and, therefore, contributed little to the overall body of evidence. The exceptions to this were in the field of guideline implementation, where there have been randomised controlled trials and systematic reviews, and the studies of prescribing in primary care.

In contrast, much of the *in-vitro* evidence results from experiments performed in standardised conditions where well-controlled experiments can be designed. However, it is difficult to relate the value of such evidence to clinical situations and there appears to be no standard methodology for doing so. Mathematical modelling in bacterial population genetics is even more difficult to evaluate, but has the potential to provide answers unobtainable in any experimental situation.

The difficulties noted in undertaking this systematic review were compounded by the limited time available. It is also of note that similar problems – the paucity of good evidence and the difficulty of adapting scoring schemes devised for clinical trials – were encountered by the review being undertaken by the Advisory Committee on the Microbiological Safety of Foods.

20.5 PAPERS APPRAISED

20.5.1 IN VITRO CONTROLLED EXPERIMENTS AND MATHEMATICAL MODELS

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
222	Lenski RE 1997	The cost of antibiotic resistance – from the perspective of a bacterium	Review of *in-vitro* experiments	Costs of antibiotic resistance in bacteria are subject to evolutionary change and reduce over time due to natural selection	1
224	Bouma JE, Lenski RE 1988	Evolution of a bacterial/plasmid association	*In-vitro* controlled experiment	New plasmid-bearing *E. coli* inferior competitor to plasmid-free strain in absence of antibiotic. After 500 generations in presence of chloramphenicol genetic adaptation had occurred in chromosome so evolved plasmid-bearing bacteria had competitive advantage even in absence of antibiotic	1
278	Lenski RE, Simpson SC, Nguyen TT 1994	Genetic analysis of a plasmid-encoded, host genotype-specific enhancement of bacterial fitness	*In-vitro* controlled experiment	Tetracycline resistance is actually beneficial to the evolved host bacteria in the absence of antibiotic, making it competitively superior to its plasmid-free counterpart	1
279	Modi RI, Adams J 1991	Co-evolution in bacteria-plasmid populations	*In-vitro* controlled experiment	After 800 generations cost of carriage of a plasmid encoding resistance for ampicillin and tetracycline in *E. coli* significantly reduced, due to changes in both bacterial and plasmid genomes	1

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
218	Schrag SJ, Perrot V 1996	Reducing antibiotic resistance	*In-vitro* controlled experiment	Chromosomal mutations in rpsL gene of *E. coli* confer resistance to streptomycin, but at cost of altered ribosomes and slower protein synthesis. After >200 generations this cost is reduced due to secondary mutations elsewhere, without change in streptomycin resistance	1
280	Cohan FM *et al* 1994	Amelioration of the deleterious pleiotropic effects of an adaptive mutation in *Bacillus subtilis*	*In-vitro* controlled experiment	Mutations causing rifampicin resistance occur in gene coding for RNApolymerase, reducing competitive fitness. Cost varies with both mutation and strain of *B. subtilis*, so should be reduced over time due to natural selection	1
281	Sundin GW, Bender CL 1996	Dissemination of the strA-strB streptomycin resistance genes among commensal and pathogenic bacteria from humans, animals and plants	*In-vitro* controlled experiment	Resistance persists widely in nature. The genes encoding for streptomycin resistance have been recently disseminated by transfer between human-, animal- and plant-associated bacteria	2
282	Roberts M, Elwell LP, Falkow S 1977	Molecular characterization of two β-lactamase-specifying plasmids isolated from *Neisseria gonorrhoeae*	*In-vitro* controlled experiment	Stability of penicillin resistance in *N. gonorrhoeae* plasmids increased over time	2
219	Schrag SJ *et al* 1997	Adaptation to the fitness costs of antibiotic resistance in *Escherichia coli*	*In-vitro* controlled experiment	Second site mutations compensate for fitness costs of streptomycin resistance in *E. coli* to produce a competitive advantage over sensitive strains. The resistance sequences had not changed over 10,000 generations	1
283	Borman *et al* 1996	Resistance of HIV-I to protease inhibitors. Selection of resistant mutations in the presence and absence of the drug	*In-vitro* controlled experiment	Resistant strains of HIV-1 did not revert to wild type when serially passaged in drug-free conditions. Secondary mutations continued to emerge, improving both replicative capacity and resistance	1
226	Levin BR, Lipsitch M, Perrot V *et al* 1997	The population genetics of antibiotic resistance	Mathematical modelling	Frequencies of resistant bacteria are related to antibiotic usage, but decline in rates after restrictions would be very slow and subject to rapid reversal on re-introduction	1
225	Bonhoeffer S, Paulous S, Clavel F 1997	Evaluating treatment protocols to prevent antibiotic resistance	Mathematical modelling	Long-term benefit from first use to high resistance levels is almost independent of pattern of use. When more than one antibiotic is used the optimum strategy is to use both drugs in combination	2

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
284	Lipsitch M, Levin BR 1997	The population dynamics of antimicrobial chemotherapy	Mathematical modelling	Model predicts resistance will not emerge during treatment if resistant mutants are not present initially and the average net rate of decline is comparable to rate of cell division, but sustained exposure to lower doses will select for resistance. Random non-adherence to regimen can be compensated for by more potent drug combinations	2

20.5.2   EFFECT OF ANTIBIOTIC USE ON RESISTANCE PATTERNS

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
228	Levy SB, Marshall B, Schluederberg S, Rowse D, Davis J 1988	High frequency of antibiotic resistance in human fecal flora	Cross-sectional survey	Seven agents in 600 subjects, healthy, ambulatory and hospitalised: high rate of resistance regardless of recent antibiotic therapy (10% of those with no recent history had one or more resistant strains, and >50% of those taking antibiotics). Frequent multi-resistance found	IV
285	Hart CA 1998	Antibiotic resistance: an increasing problem?	Editorial	Resistance problem is increasing, but genes and mechanisms existed before antibiotics were ever used. Inappropriate to apportion blame but should reconsider control of infection practice	
286	D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A 1998	Effect of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials	Systematic review and meta-analysis of RCTs	Prophylaxis with a combination of topical and systemic antibiotics can reduce respiratory tract infections and overall mortality in critically ill patients. No conclusion on risk of antibiotic resistance due to lack of valid data	IA
287	Working Party of the British Society for Antimicrobial Chemotherapy 1994	Hospital antibiotic control measures in the UK	Postal survey	Majority of responding hospitals had policies: 51% for prophylaxis, 62% therapy and 79% formulary, but compliance was monitored in only 40% and actively controlled in only 50% of these. Only 11% had formal audit	IV

20.5.3   IMPACT OF ANTIBIOTIC POLICIES ON RESISTANCE LEVELS

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
242	Betts RF, Valenti WM, Chapman SW *et al* 1984	Five-year surveillance of aminoglycoside usage in a university hospital	Prospective study	Following a change from gentamicin to amikacin as the primary aminoglycoside, resistance to gentamicin and tobramycin showed a statistically significant decrease in several gram-negative organisms	IIB
234	Kataja J, Huovinen P, Muotiala A *et al* 1998	Clonal spread of group A streptococcus with the new type of erythromycin resistance. Finnish Study Group for Antimicrobial Resistance	Retrospective survey	The new erythromycin resistance reported in Finland in the 1990s is mostly from a single clone	IIIC
233	Seppala H, Klaukka T, Vuopio-Varkila J *et al* 1997	The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococcus in Finland. Finnish Study Group for Antimicrobial Resistance	Retrospective survey	National policy reduction in macrolide antibiotics in community led to decrease in frequency of resistance in isolates	IIIC
288	Seppala H, Klaukka T, Lehtonen R, Nenonen E, Huovinen P 1997	Erythromycin resistance of group A streptococci from throat samples is related to age	Retrospective survey	Risk of resistance decreased significantly with increasing age by 1% a year, possibly due to different prescribing practices	IV
19	Huovinen P, Seppala H, Kataja J, Klaukka T 1997	The relationship between erythromycin consumption and antibiotic resistance in Finland. Finnish Study Group for Antimicrobial Resistance	Review of retrospective studies	Erythromycin resistance in isolates significantly linked to local consumption. 83% of isolates were a single clone. Following new prescribing guidelines macrolide consumption fell by 40%	IV
289	Seppala H *et al* 1995	Outpatient use of erythromycin; link to increased erythromycin resistance in group A streptococci	Cross-sectional survey	206 health authorities: proportion of isolates resistant to erythromycin in 1992 increased significantly with local out-patient consumption in 1991	IV
290	Cullman W 1996	Comparative evaluation of orally active antibiotics against community acquired pathogens: results of eight European countries.	Multi-centre cross-sectional survey	>13,000 isolates from 37 centres. For many species % resistant similar across Europe, but high levels of penicillin G-resistant *S. pneumoniae* in Spain and Hungary and ampicillin resistant *H. influenzae* in Spain	IV
291	Nissinen A, Gronroos P, Huovinen P *et al* 1995	Development of beta-lactamase-mediated resistance to penicillin in middle ear isolates of *Moraxella catarrhalis* in Finnish children 1978–1993	Cross-sectional survey	Bimodal increase in resistance; 0–60% up to 1983 and from 60–80% in 1988–90. Substantial increase in cephalosporin use in community coincided with second increase	IV

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
292	Nissinen A, Leinonen M, Huovinen P *et al* 1995	Antimicrobial resistance of *Streptococcus pneumoniae* in Finland 1987–1990	Cross-sectional survey	Isolates from middle ear fluid of children with otitis media and throat swabs from healthy children. Six multi-resistant strains identified, 85% from three common serogroups	IV
236	Manninen R, Huovinen P, Nissinen A *et al* 1997	Increasing antimicrobial resistance in *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* in Finland	Cross-sectional survey	Levels rose including erythromycin resistance in pneumococci, which increased from 0.6% in 1990 to 2.5% in 1995	IV
270	King JW, White MC, Todd JR, Conrad SA 1992	Alterations in the microbial flora and in the incidence of bacteremia at a university hospital after adoption of amikacin as the sole formulary aminoglycoside	Prospective study comparing low use with high frequency usage	Rates of resistance to gentamicin, tobramycin and amikacin in gram-negative isolates fell by ~50% following the intervention. Incidence of bacteraemia also decreased	IIC?
237	Stephenson J 1996	Icelandic researchers are showing the way to bring down rates of antibiotic-resistant bacteria	News report of conference paper by Kristinsson	Great increase in penicillin-resistant pneumococci (PRP) in Iceland to 1993 especially in children's day-care. Major publicity campaign to public and physicians. Parents encouraged not to send sick children. Sales fell from 1990 on. Resistance declined from 20% in 1992 to 15% in 1995 (not significant)	?
293	Asensio A, Guerrero A, Quereda C, Lizan M, Martinez-Ferrer M 1996	Colonisation and infection with methicillin resistant *Staphylococcus aureus*: associated factors and eradication	Retrospective case-control and cohort studies	Six factors associated independently with MRSA colonisation/infection: age, ward (OD surgical 1/ ICU 60) previous or long hospitalisation, coma and invasive procedures. Antibiotic therapy not independent risk factor. Reduce rates by identifying high risk, prompt discharge and control of infection in invasive procedures	IIIA
17	Muder RR, Brennen C, Drenning SD, Stout JE, Wagener MM 1997	Multiple antibiotic resistant gram-negative bacilli in a long-term care facility: a case-control study of patient risk factors and prior antibiotic use	Retrospective case-control study	Acquisition of resistance associated with prior antibiotic exposure	IIIC
294	Brennen C *et al* 1998	Vancomycin resistant *Enterococcus faecium* in a long-term care facility		24 of 36 patients with VREF had it on transfer from acute care. 17 also had MRSA. Treatment of VREF colonisation with antimicrobial agents prolonged carriage	IIIC

20.5.4 GUIDELINE IMPLEMENTATION AND CHANGING CLINICAL PRACTICE

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
268	NHS centre for Reviews and Dissemination, University of York and Nuffield Institute for Health, University of Leeds 1995	Effective Health Care Bulletin. Implementing clinical practice guidelines: can guidelines be used to improve clinical practice?	Systematic review of 91 guideline implementation evaluations	Practice guidelines can change professional behaviour and improve process and outcome of care. 81 showed improvements in care and 12/17 in outcome	IA
266	Grimshaw J, Russell I 1993	Effect of clinical guidelines on medical practice – a systematic review of rigorous evaluations	Systematic review	Review of implementation of 59 guidelines. 55 resulted in significant improvements in care	IA
269	Grol R 1997	Beliefs and evidence in changing clinical practice	Review/ comment	Implementing change requires good planning and several interventions. Obstacles to change should be identified	
295	Weingarten SR, Riedinger MS, Hobson P *et al* 1996	Evaluation of a pneumonia practice guideline in an interventional trial	Prospective controlled trial	Guideline provided information on switching patients from parenteral to oral antibiotics and early discharge. No significant difference in care (majority conformed to guideline) or outcomes	IIB

20.5.5 IMPROVING HOSPITAL PRESCRIBING OF ANTIMICROBIAL AGENTS

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
250	Pestotnik SL, Classen DC, Evans RS, Burke JP 1996	Implementing antibiotic practice guidelines through computer assisted decision support: clinical and financial outcomes	Prospective descriptive epidemiology and financial analysis	Computer-assisted decision-support programmes using local clinically derived guidelines improved antibiotic use, reduced costs and stabilised resistance levels	IIB
251	Evans RS, Pestotnik SL, Classen DC *et al* 1998	A computer-assisted management programme for antibiotics and other anti-infective agents	Prospective interventional study in ITU with retrospective controls	Programme use reduced antibiotic susceptibility mismatches and excess doses. Full compliance caused shorter stays and lower drug and hospital costs	IIC
296	Evans RS, Classen DC, Pestotnik SL, Lundsgaarde HP, Burke JP 1994	Improving empiric antibiotic selection using computer decision support	Prospective controlled trial	The computer programme helped physicians to order the optimum regimen significantly more often	IIB

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
216	McGowan JE 1994	Do intensive hospital antibiotic control programs prevent the spread of antibiotic resistance?	Review	Most studies do not have susceptibility as an outcome and have problems of bias and confounding. Intensive control programmes for drug–organism pairs in a few hospitals were associated with increased susceptibility, which reversed rapidly when controls were relaxed. Properly conducted multi-centre studies are required	IIIC
16	McGowan JE 1996	Does antibiotic restriction prevent resistance?	Review	Association between antimicrobial usage and resistance is likely to be causal. Educational efforts alone have failed to be effective on a large scale or in the long term	
18	Shlaes DM, Gerding DN, John JF *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	Review and guidelines	Appropriate usage including optimal selection, dosage and duration of treatment and control of use will prevent or slow emergence of resistance	IIC
58	Archibald L, Phillips L, Monnet D, McGowan JE, Tenover F, Gaynes R 1997	Antimicrobial resistance in isolates from inpatients and outpatients in the United States: increasing importance of the intensive care unit	Cross-sectional survey	% of resistant isolates decreased from ICU patients through other in-patients to out-patient samples over a range of antimicrobial agents and organisms in eight hospitals. Resources allocated to control should be focused on hospitals and especially ICUs	IV
188	Baquero F 1996	Antibiotic resistance in Spain: what can be done?	Review/health policy statement	Strategies for improving surveillance of resistance, monitoring antibiotic consumption and influencing producers, prescribers and consumers	–
297	Sturm AW 1990	Effects of a restrictive antibiotic policy on clinical efficacy of antibiotics and susceptibility patterns of organisms	Retrospective study following policy change	Restrictive antibiotic policy led to cure in 88% with initial therapy and further 7% with change of drugs, but failure in 5%. No change in resistance patterns over 2-month evaluation period	IIIC
298	Goldmann DA, Weinstein RA, Wenzel RP *et al* 1996	Strategies to prevent and control the emergence and spread of antimicrobial resistant micro-organisms in hospitals	Consensus statement and review	Highlights excessive prescribing and failure to use basic infection control techniques. Provides strategies to optimise usage and monitor development of resistance in a hospital, with suggested process and outcome measures	–

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
271	Pear SM, Williamson TH, Bettin KM, Gerding DN, Galgiani JN 1994	Decrease in nosocomial *Clostridium difficile*-associated diarrhoea by restricting clindamycin use	Surveillance and retrospective case control	Nosocomial outbreak was controlled by analysis of antibiotic usage, identification of a clindamycin-resistant strain and then restriction of clindamycin. Frequency of isolation of this strain subsequently declined (p <0.001)	IIIB
299	Moller JK 1989	Antimicrobial usage and microbial resistance in a university hospital during a seven-year period	Retrospective survey of hospital and community	Resistance in *S. aureus* and *E. coli* stable overall, but increased in *S. epidermidis* from 29% in 1981 to 43% in 1987. Correlation between specific usage and resistance when co-selection from other antimicrobial agents included	IIIC
300	Courcol RJ, Pinkas M, Martin GR 1989	A seven year survey of antibiotic susceptibility and its relationship with usage	Retrospective survey in hospital	Significant correlation between antibiotic usage and increasing resistance, especially in cephalosporin	IV
301	Olson B, Weinstein RA, Nathan C, Chamberlin W, Kabins SA 1984	Epidemiology of endemic *Pseudomonas aeruginosa*: why infection control efforts have failed	Detailed survey in ICU	Many patients arrived colonised, but this was unrecognised, despite frequent throat and rectal cultures. Cross-infection rare	IIIB
15	Chow JW, Fine MJ, Shlaes DM *et al* 1991	Enterobacter bacteremia: clinical features and emergence of antibiotic resistance to therapy	Prospective multicentre observational study	Previous administration of third-generation cephalosporins more likely to be associated with resistance than other antimicrobial agents	IIC
20	Manian FA, Meyer L, Jenne J, Owen A, Taff T 1996	Loss of antimicrobial susceptibility in aerobic gram-negative bacilli repeatedly isolated from patients in intensive-care units	Prospective observational study	Loss of sensitivity in repeat AGNB isolates is common and related to prior antibiotic use. Minimising use of antibiotics in ICUs is important to help reduce risk of resistance development	IIC
127	Vincent JL, Bihari DJ, Suter PM *et al* 1995	The prevalence of nosocomial infections in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study	1-day point prevalence study	ICU infection is common and often associated with resistant strains. Risk factors include length of stay, ventilation, trauma and catheterisation	IV
302	Johnson AP, Speller DC, George RC, Warner M, Domingue G, Efstratiou A 1996	Prevalence of antibiotic resistance and serotypes in pneumococci in England and Wales: results of observational surveys in 1990 and 1995	2-week observational surveys of PHLS laboratories	Resistance to penicillin and erythromycin increased. No change in other organisms. No resistance to rifampicin or vancomycin detected during study periods	IV

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
303	Baquero F 1996	Trends in antibiotic resistance of respiratory pathogens: an analysis and commentary on a collaborative surveillance study	Retrospective multicentre survey: resistance vs prescription data for 1992 and 1993	Complex situation but in general countries with highest per capita consumption also have highest resistance levels. Definite stages of development from susceptibility to very high resistance	IIIB
144	McNulty C, Logan M, Donald IP 1997	Successful control of *Clostridium difficile* infection in an elderly care unit through use of a restrictive antibiotic policy	Observational study of antibiotic usage and infection rates	Outbreak controlled by combination of infection control measures and strict prescribing	IV
304	Acar JF 1997	Consequences of bacterial resistance to antibiotics in medical practice	Review	Costs of resistance include extra bed days and diagnostic tests in addition to higher antibiotic costs	–
305	Barie PS 1998	Antibiotic-resistant gram-positive cocci: implications for surgical practice	Review	Use of broad-spectrum antibiotics selects for resistance. Rampant inappropriate use of vancomycin must be curtailed and infection control precautions tightened	IV
306	Rho JP, Yoshikawa TT 1995	The cost of inappropriate use of anti-infective agents in older patients	Review	High levels of inappropriate prescribing found in several studies. Likely consequences are poor compliance, adverse reactions and selection for resistance	IV
307	Sutherland R 1991	Beta-lactamase inhibitors and reversal of antibiotic resistance	Review	Development of clavulanate and other similar inhibitors (not reduction in prevalence of resistance)	–
308	Rubin LG, Tucci V, Cercenado E, Eliopoulos G, Isenberg HD 1992	Vancomycin-resistant *Enterococcus faecium* in hospitalised children	Survey and case control study	High prevalence of VRE amongst paediatric oncology patients, associated with length of stay and administration of vancomycin and other antibiotics. Prevention associated with contact isolation and restriction of vancomycin use	IV
309	Evans ME *et al* 1996	Vancomycin in a university medical centre: comparison with hospital infection control practices advisory committee guidelines	1-month prospective survey of all patients given vancomycin	Only 35% of prescriptions conformed to guidelines. Main reason was failure to obtain cultures	IV
310	Harbarth S, Rutschmann O, Sudre P, Pittet D 1998	Impact of methicillin resistance on the outcome of patients with bacteremia caused by *Staphylococcus aureus*	Cohort and case control studies	Methicillin resistance in patients with *S. aureus* bacteraemia had no significant impact on mortality after adjustment for major confounders (age and length of stay)	IIIB

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
21	Parry MF, Panzer KB, Yukna ME 1989	Quinolone resistance. Susceptibility data from a 300-bed community hospital	Prospective survey over 4 years	Resistance levels rose with increasing usage and 72% of isolates were from patients who had had a fluoroquinolone in the previous month	IV
311	Zakrzewska-Bode A, Muytjens HL, Liem KD, Hoogkamp-Korstanje JA 1995	Mupirocin resistance in coagulase-negative staphylococci, after topical prophylaxis for reduction of colonization of central venous catheters	Survey plus small prospective series	After 5 years of routine application, resistance was observed in 42% of isolates from NICU – fell to 21% after 5 mupirocin-free months and 13% after 1 year	IV
312	Conus P, Francioli P 1992	Relationship between ceftriaxone use and resistance of *Enterobacter* species	Retrospective survey	Compared consumption and evolution of resistance over 4 years. Consumption trebled and resistance in isolates rose from 10 to 27%. No changes in hospital hygiene and no epidemics during study period	IV
313	Bergmans DC, Bonten MJ, Gaillard CA *et al* 1997	Indications for antibiotic use in ICU patients: a one-year prospective surveillance	Prospective survey	53% of infections were ICU-acquired, 99% in intubated patients. 59% of antibiotics were prescribed for bacteriologically proven infections. Prevention of RTI most effective mode of reduction of antibiotic use	IV
314	Boyce JM, Opal SM, Potter-Bynoe G, Medeiros AA 1993	Spread of methicillin-resistant *Staphylococcus aureus* in a hospital after exposure to a health care worker with chronic sinusitis	Retrospective study	Cases in an epidemic of MRSA were found to be significantly more likely to have had contact with a respiratory therapist with chronic sinusitis with the same strain. Plasmid DNA of isolates had the same digestion pattern. Eradication of the sinusitis and nasal carriage, and implementation of general control measures terminated the outbreak	IIIC
14	Fish DN, Piscitelli SC, Danziger LH 1995	Development of resistance during antimicrobial therapy: a review of antibiotic classes and patient characteristics in 173 studies	Review	Resistance was most common in intensive care units or ventilated patients, and in studies in teaching hospitals	III
315	Anglim AM, Klym B, Byers KE, Scheld WM, Farr BM 1997	Effect of a vancomycin restriction policy on ordering practices during an outbreak of vancomycin resistant *Enterococcus faecium*	Audit of vancomycin use pre- and post-policy implementation	Use compared with HICPAC guidelines from CDCP, Atlanta. Initially 61% inappropriate according to criteria, falling to 30% at follow-up. Overall use fell by 50%	IIIB

20.5.6 RESISTANCE IN THE COMMUNITY

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
238	Kristinsson KG 1995	Epidemiology of penicillin resistant pneumococci in Iceland	Review	Rapid spread of PRP in Iceland may have been facilitated by high antimicrobial consumption in day-care centres for small children. Most resistant infections came from a clone originating in Spain	IV
239	Kristinsson KG 1997	Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci	Review	Propaganda against overuse, led to reduction in usage and subsequent reduction in PRP	IV
316	van den Bogaard AE 1997	Antimicrobial resistance – relation to human and animal exposure to antibiotics	Letter/survey	Antimicrobial agents for animal use much cheaper than for humans so expenditure unreliable guide to usage. In 1990 human dosage in Holland was 100 mg active substance/kg body weight/year in contrast to 125 mg/kg/year for poultry and 430 mg/kg/year for pigs, mostly in animal husbandry rather than veterinary medicine	IV
240	Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S 1996	Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross-sectional prevalence study	Cross-sectional prevalence study	Antimicrobial use (individual and total) is strongly associated with nasopharangeal carriage in children	IV
272	McCaig LF, Hughes JM 1995	Trends in antimicrobial drug prescribing among office-based physicians in the United States	National sample survey on prescribing patterns	Increasing trend towards more expensive broad-spectrum antimicrobial agents and away from penicillins. This has impact on all patients due to higher costs and emerging resistance	IV
317	Stuart JM, Robinson PM, Cartwright K, Noah ND 1996	Antibiotic prescribing during an outbreak of meningococcal disease	Survey of GP prescribing rates in areas of high and low incidence	Erythromycin prescribing significantly higher in high incidence towns, possibly due to increased consultations for URTI, but may have contributed to increased acquisition	IV
318	Hammond ML, Norriss MS 1995	Antibiotic resistance among respiratory pathogens in preschool children	Survey in socio-demographically matched areas of Melbourne and Sydney	Resistance in pre-school children significant and possibly increasing	IV
154	Nyquist AC, Gonzales R, Steiner JF, Sande MA 1998	Antibiotic prescribing for children with colds, upper respiratory tract infections and bronchitis	Representative national survey	Outcomes were principal diagnoses and prescriptions. Antibiotics were prescribed for 44% children with colds, 46% with URTIs and 75% with bronchitis	IV

20.5.7 PRIMARY CARE PRESCRIBING BEHAVIOUR

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
155	Macfarlane JT, Holmes WF, Macfarlane RM 1997	Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomised controlled study of patients in primary care	Randomised controlled trial	Informing previously well patients about LRTI reduced reconsultations. It is also likely to reduce antibiotic usage and future consultation habits	IA
156	Holmes WF, Macfarlane JT, Macfarlane RM *et al* 1997	The influence of antibiotics and other factors on reconsultation for acute lower respiratory tract illness in primary care	Prospective study	Reconsultation is common in acute LRTI, associated with previous consulting habit, illness or dyspnoea, but not prescription of antibiotics at the index visit	IIB
157	Macfarlane J, Lewis SA, Macfarlane R, Holmes W 1997	Contemporary use of antibiotics in 1089 adults presenting with acute lower respiratory tract illness in general practice in the UK: implications for developing management guidelines	Prospective study	115 GPs prescribed antibiotics to three-quarters of patients. In addition to underlying disease and clinical factors, other factors influencing prescribing were patient pressure and social factors, and GP work pressure and previous experience of the patient, especially if the GP felt antibiotics were not indicated clinically	IIC
158	Macfarlane JT, Holmes WF Macfarlane R, *et al* 1997	Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study	Prospective study	Patients presenting with acute lower respiratory tract illness expect antibiotics and have significant influence on prescribing, even when antibiotics are not indicated	IIB
273	Ekedahl A, Andersson SI, Hovelius B, Molstad S, Liedholm H, Melander A 1995	Drug prescription attitudes and behaviour of general practitioners. Effects of a problem-oriented educational programme	Controlled prospective evaluation of educational programme	Producer-independent, problem-oriented group education programme did change attitudes and produced significant and sustained changes in prescribing and drug sales	IIB
275	Molstad S, Ekedahl A, Hovelius B, Thimansson H 1994	Antibiotics prescription in primary care: a 5-year follow-up of an educational programme	Controlled prospective evaluation of educational programme	Overall enduring reduction in prescriptions especially for broad-spectrum antibiotics. GPs were also aware that computer records of diagnosis and treatment enabled individual audit	IIB
277	Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL 1997	Reattendance and complications in a randomised controlled trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics	Randomised controlled trial	Complications and early return resulting from no or delayed prescription are rare. Current and previous antibiotic prescribing for sore throat increases likelihood of reattendance	IA

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
164	Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL 1997	Open randomised trial of prescribing strategies for managing sore throat	Randomised controlled trial	Prescribing antibiotics enhances patients' belief in them and intention to consult in future, compared with no or delayed prescription	IA
319	Britten N, Ukoumunne O 1997	The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: a questionnaire survey	Prospective survey of patients and retrospective survey of doctors in SE London	In area of low prescribing and high expectations, doctors' perceptions of patients' expectations was strongest predictor of prescribing decision	IIIC
276	Armstrong D, Reyburn H, Jones R 1996	A study of general practitioners' reasons for changing their prescribing behaviour	Qualitative analysis of semi-structured interviews	Interviewees identified recent specific changes. Major factors included: evidence, willingness to change and a challenging clinical event	IV
159	Bradley CP 1992	Factors which influence the decision whether or not to prescribe: the dilemma facing general practitioners	Focused interviews of GPs	Decision hardest for respiratory disease, skin problems and psychiatric conditions. Patient factors included socio-economic factors and doctor–patient relationship. Doctor factors included previous clinical experience, logistics, peer- and self-expectations	IV
160	Bradley CP 1992	Uncomfortable prescribing decisions: a critical incident study	Focused interviews of GPs	Main reasons for decision: patient expectations, clinical appropriateness, GP–patient relationship and precedents	IV
161	Webb S, Lloyd M 1994	Prescribing and referral in general practice: a study of patients' expectations and doctors' actions	Prospective survey of patients and retrospective survey of doctors	GP actions strongly associated with patient expectations, both in prescribing and hospital referral	IIIC
164	Steffensen FH, Schonheyder HC, Sorensen HT 1997	High prescribers of antibiotics among general practitioners – relation to prescribing habits of other drugs and use of microbiological diagnostics	Retrospective survey of prescriptions and use of diagnostics	15-fold range between GPs. Positive predictors were high prescribers of other drugs, and high users of cultures and urine tests. High use of throat cultures was a negative predictor	IV
163	Macfarlane J, Prewett J, Rose D et al 1997	Prospective case-control study of role of infection in patients who reconsult after initial antibiotic treatment for lower respiratory tract infection in primary care	Prospective observational study with nested case-control	Active infection is rare at reconsultation and another antibiotic prescription thus not indicated. Patient perception is more important than infection – two-thirds obtained another antibiotic	IIB

20.5.8 OTHER REFERENCES:

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
320	Solomkin JS 1996	Antimicrobial resistance: an overview	Editorial	Lack of documentary evidence that resistance harms individual patients in ICU. Conflict between individual and wider good. Compliance with basic hygiene very poor	–
321	Bohnen J 1998	Antibiotic therapy for abdominal infection	Clinical review	Little information on promotion of resistance in this condition	–
274	Webster J, Faoagali JL, Cartwright D 1994	Elimination of methicillin-resistant *Staphylococcus aureus* from a neonatal intensive care unit after handwashing with triclosan	Survey of new MRSAcases after policy change	No other procedural changes. No new isolates reported after discharge of last colonised infant. Cost-saving due to reduction in vancomycin use	IV
322	Haley RW, Cushion NB, Tenover FC *et al* 1995	Eradication of endemic methicillin-resistant *Staphylococcus aureus* from a neonatal intensive care unit	Retrospective survey	Triple dye applied to cords of neonates in intermediate care but not NICU, and rate of MRSA decreased in intermediate care only. Extension to NICU and dedicated infection control nurse led to near zero colonisation and infection in both areas	IIIB
323	Payne DN *et al* 1998	Antiseptics; a forgotten weapon in the control of antibiotic resistant bacteria in hospital and community settings	*In-vitro* experiment	4 antiseptics tested against various strains: all showed some effect against *E. coli, E. coli* O157, *S. aureus*, MRSA, *E. hirae* and VRE	3
324	Hancock RE 1997	The role of fundamental research and biotechnology in finding solutions to the global problem of antibiotic resistance	Conference presentation	Outlines variety of novel approaches including recombinant cationic peptides	
325	Bax RP 1997	Antibiotic resistance: a view from the pharmaceutical industry	Conference presentation	Development influenced by market opportunities. All new products since 1960 are modifications of existing structures. Problems with clinical trials of antimicrobial agents due to patients' needs. Need to develop more sophisticated outcome measures than cure and eradication	
326	Couper MR 1997	Strategies for the rational use of antimicrobials	Conference presentation	WHO preparing to assist countries to develop rational policies. Need to monitor drug use and resistance patterns	

REF. NO.	AUTHOR(S) AND YEAR	TITLE	STUDY TYPE/ DESIGN	RESULTS	GRADE
327	O'Brien TF 1997	The global epidemic nature of antimicrobial resistance and the need to monitor and manage it locally	Conference presentation	Over 1000 resistant genes now identified. May delay emergence by using fewer antimicrobial agents, and delay spread by good hygiene, infection control and avoidance of agents likely to select for resistant strains. Global problem requires local solutions	
328	Goldmann DA, Huskins WC 1997	Control of nosocomial antimicrobial resistant bacteria: a strategic policy for hospitals world wide	Conference presentation	Emphasises need for better basic hygiene precautions; thorough hand-washing and use of gloves, etc. Multidisciplinary efforts supported by management should be fully monitored	
329	Hughes JM, Tenover FC 1997	Approaches to limiting emergence of antimicrobial resistance in bacteria in human populations	Conference presentation	Prevention and control will require sophisticated surveillance, using epidemiological, statistical and molecular techniques	
330	Helmuth R, Protz D 1997	How to modify conditions limiting resistance in bacteria in animals and other reservoirs	Conference presentation	Antimicrobial agents should be used only by a doctor or vet, and are not suitable for eradication of a pathogen from an environment or to replace poor hygiene	
331	Spratt BG, Duerden BI, *et al* 1997	Antibiotic resistance; the threat to international health	Conference report		
332	Michel M, Gutmann L 1997	Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: therapeutic realities and possibilities	Review	Proposed schemes for medical management, based on preventive measures for colonisation/ carriage. Vancomycin alone or in combination (depending on site and strain) for MRSA and various combinations including amoxycillin and/or gentamicin depending on susceptibility	III
333	Levin BR, Antia R, Berliner E *et al* 1998	Resistance to antimicrobial chemotherapy: a prescription for research and action	Conference workshop report and update	Even with more prudent use resistance will not decline quickly if at all. Need to husband existing drugs and implement other means of infection control	

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PRESCRIBING IN THE COMMUNITY

Patients with minor infections mostly present to GPs; consequently, 80% of UK human prescribing is in the community. This Report, therefore, concentrates on community prescribing of antimicrobial agents.

There should be a national Campaign on Antibiotic Treatment (CAT) in primary care on the theme of: 'Four things you can do to make a difference' (see Box). The CAT must be matched by a National Advice to the Public (NAP) campaign aimed specifically at supporting the initiative in primary care. A key feature of the NAP campaign should be to highlight the benefits of 'cherishing and conserving your normal bacterial flora'. Further support for appropriate prescribing in primary care should be provided by developing and promulgating evidence-based national guidelines for the management of certain infections, under the aegis of the National Institute for Clinical Excellence. Such national guidelines should be adapted for local use during the development of Health Improvement Plans. To make the incorporation of the guidelines into everyday practice as effort-free as possible they should be integrated within computerised decision-support systems.

FOUR THINGS YOU CAN DO:

- no prescribing of antibiotics for simple coughs and colds
- no prescribing of antibiotics for viral sore throats
- limit prescribing for uncomplicated cystitis to 3 days in otherwise fit women
- limit prescribing of antibiotics over the telephone to exceptional cases

PRESCRIBING IN HOSPITALS

Hospital prescribing accounts for c. 20% of human prescribing of antimicrobial agents in the UK; nevertheless, resistance problems are greatest in hospitals and infections may be life-threatening. Although prescribing in hospitals poses some different issues from those in primary care, hospital clinicians would benefit as much as GPs from the availability of computer-aided decision-support systems.

Studies should be undertaken in selected hospitals to develop and test one or more prototype decision-support systems. Systems should include information from local antimicrobial sensitivity profiles, these, in turn, should feed into regional and national surveillance databases.

PRESCRIBING GUIDELINES

Prescribing guidelines should be quality evidence-based documents. They are often the first source of information for inexperienced prescribers. National guidelines, suitably adapted in response to local resistance patterns, could be integrated into decision-support systems.

Local prescribing information should, wherever possible, be harmonised with prescribing information in the British National Formulary (BNF) and other formularies.
Guidelines and formularies should also take account of the proposed national evidence-based guidelines to be produced under the aegis of the National Institute for Clinical Excellence.
Local prescribing guidelines should take their cue from these national guidelines.
All such local guidelines should include, as a minimum, advice on drug, dose, frequency and duration.

INTERNATIONAL CO-OPERATION

Resistant bacteria spread between countries, the UK is not isolated from the greater resistance problems that exist in other parts of the world, for example, Southern Europe.

Every effort should be made by the Government in international fora, particularly in the European Union, to raise the profile of antimicrobial resistance as a major public health issue meriting priority action.

SURVEILLANCE OF RESISTANCE

Effective surveillance is critical to understanding and controlling the spread of resistance. Not only is surveillance essential for monitoring the existing situation, it allows the effects of interventions to be evaluated.

A national strategy for resistance surveillance should be developed and implemented as swiftly as possible, covering the whole of the UK.

RESEARCH

Antimicrobial resistance has been of low priority for Research Councils and scored poorly in the recent Research Assessment Exercise.

Research into antimicrobial resistance should become a high priority for all funding bodies concerned with health care and biomedical research.

EDUCATION

The development of guidelines and their widescale introduction into clinical practice will have important and beneficial spin-offs for the education of health care professionals involved in antimicrobial prescribing. The whole population would benefit from enhanced education about the benefits and disadvantages of antimicrobials.

Greater emphasis should be placed on teaching about antimicrobial prescribing in medical and dental schools as well as in the undergraduate curricula for pharmacists and nurses.
Teaching about antimicrobials should be better integrated with teaching about the infections for which they are used.
This enhanced emphasis on education in antimicrobial use should be carried over into continuing medical, dental and professional education and development. Similar concepts apply in the field of veterinary medicine.
In addition to health education material aimed at adults, teaching about antibiotics should be included as part of health education in the National Curriculum.

HYGIENE, INFECTION CONTROL AND CROSS-INFECTION

Infection control, although intimately bound up with problems of antimicrobial resistance – particularly in health care environments – was outside the Terms of Reference of the Sub-Group. Nevertheless, it is fundamental to preventing the spread of resistant organisms, not only in hospitals but also in the community.

Consideration should be given to producing guidance on infection control in the community, especially in nursing and residential homes, similar to that which exists for hospitals.

VETERINARY AND AGRICULTURAL USE

Antimicrobials are used in therapy and prophylaxis, and as growth promoters/enhancers in animals

The use of antibiotics in veterinary practice should be guided by the same principles as for human prescribing – namely, they should be used only for clinical conditions where their use is likely to provide a genuine health benefit.
Alternative means of animal husbandry should be developed so that the use of antibiotics as growth promoters can be discontinued.

IMPLICATIONS FOR INDUSTRY

If our recommendations are followed, they should have the effect, *inter alia*, of reducing antibiotic usage. There may be financial implications for the pharmaceutical industry, upon whose profitability the development of new antibiotics depends.

Consideration should be given by the appropriate bodies to finding ways – through pricing and other mechanisms – of ensuring that investment in the development of new antibiotics remains commercially viable. Industry should be encouraged to undertake studies of optimum prescribing regimens for new antimicrobial agents, for each indication and in adults and children as appropriate. Licensing authorities should have due regard to an antimicrobial agent's potential to select for resistance as well as to its safety and efficacy.

22.1	IMPLEMENTATION OF RECOMMENDATIONS

The aim of this Report has been to produce recommendations that can constitute the first phase of a national strategy for minimising the development of antimicrobial resistance.

As part of this phase a small National Steering Group (NSG) should be established, charged with ensuring that these recommendations are implemented and that their effects on prescribing practice and on the development of resistance are monitored.

The NSG, which might need to establish a small number of expert groups to take forward specific aspects of the recommendations, should report to the Chief Medical Officer within a year on progress.

Thereafter the CMO may wish to consider asking SMAC to reconvene this Sub-Group, to provide a suitable inter-disciplinary forum for the development of the next phase of the strategy.

23   GLOSSARY OF TERMS

Acquired resistance	resistance to antimicrobial agents that develops in micro-organisms that were previously sensitive
Acute otitis media	inflammation of the middle ear commonly caused by infection
Analgesic	a drug that reduces or relieves pain
Analogue	corresponding or similar to
Antibacterial spectrum	the range of bacteria that are susceptible to a particular antibiotic
Antibiotic	a substance produced by or derived from a micro-organism, that selectively destroys other micro-organisms or inhibits their growth
Antibiotic policy	written guidance that recommends antibiotics and their dosage for treating of specific infections
Antifungal agent	an agent that can be used to treat infections caused by fungi
Antimicrobial agents	any compound that at low concentrations exerts an action against microbial pathogens and exhibits selective toxicity towards them
Antimicrobial chemotherapy	the use of to prevent or treat microbial disease
Antiseptic	a non-toxic chemical that can be used to clean skin before an operation so as to prevent infection or applied to skin to cleanse dirty wounds
Appendicectomy	surgical removal of the appendix
Asymptomatic	not showing any symptoms of a disease, although it is present
Audit	organised review by staff of current practices and comparison with predetermined standards. Action is then taken to rectify any deficiencies that have been identified in current practices. The review is repeated to see if the predetermined standards are being met
Bacilli	rod-shaped bacteria
Bacteraemia	presence of bacteria in the bloodstream
Bacteriophage	a virus that survives and multiplies in bacteria. Each type of bacteriophage attacks a particular type of bacterium
Bacterium	a single-celled micro-organism that is simpler and usually smaller than protozoa (q.v)
Blood culture	sample of blood taken from a patient with a serious infection, such as meningitis, and investigated in the laboratory to try to determine the pathogen causing infection
CCDC	Consultant in Communicable Disease Control, a doctor who is appointed by each Health Authority and who has a responsibility for the surveillance, prevention and control of infections in the community
Chromosome	the structure containing nucleic acid (DNA) that carries the genetic information of an organism
Clinical microbiologist	a person who studies the science of the isolation and identification of micro-organisms that cause disease in humans and applies this knowledge to treat, control and prevent infections in humans
Cocci	round bacteria
Cohort nursing	placing patients with the same infection together in an area of a ward to reduce the risk of the infection spreading to other patients. This is often done when there are more infected patients than single rooms available for isolation
Colonisation	the ability of some pathogens to live on or in a host without causing disease
Commensal	a member of the normal bacterial flora

Communicable disease	a disease caused by a micro-organism that can be passed from a person, animal or the environment to another susceptible individual
Community	populations, diseases or health services outside of hospitals
Compliance	the degree to which patients follow the instructions for taking a course of treatment
Concordance	the aim of concordance is to optimise health gain from the best use of medicines, compatible with what the patient desires and is capable of achieving
Contact	a person who has been exposed to a source of infection
CSF	cerebrospinal fluid: the clear watery fluid that surrounds the brain and spinal cord
Cystic fibrosis	an inherited disease in which respiratory tract infections are very common and often cause death
Denominator	the population considered to be at risk, eg the total number of people admitted to a hospital or receiving a particular antimicrobial agent. This is used to calculate rates such as incidence and prevalence
Disinfectant	a chemical that destroys or removes bacteria and other micro-organisms. Used to cleanse surgical instruments and surfaces of equipment or furniture
DNA	deoxyribonucleic acid: the genetic material of most living organisms
Efficacy	the effectiveness of an agent or a preparation or a treatment
Empirical treatment	treatment based on past experience or observation rather than the result of laboratory investigations
Endocarditis	infection of the heart valves
Enzyme	a protein that, in small amounts, speeds up the rate of a biological reaction without itself being used up in the reaction
Epidemiology	the study of the occurrence, cause, control and prevention of disease in populations
Febrile	feverish
Flora	see normal bacterial flora
Formulary	a compendium often used in hospitals to list the drugs readily available for prescribing. Some indicate the seniority of medical staff who may prescribe individual drugs
Fungus	a simple plant which lacks the green pigment chlorophyll. Some fungi cause local infections such as thrush or athlete's foot, but may also cause serious infections in immunocompromised people
Ganglion	an aggregation of nerve cell bodies
Gene	the basic unit of genetic material
Genomics	technique involving sequencing the entire chromosomes of bacteria
GP	general practitioner
Gram's stain	a dye that is used to stain bacteria to aid identification when viewed with a microscope
Gram-negative	bacteria that are stained red by Gram's stain
Gram-positive	bacteria that are stained violet by Gram's stain
ICU	intensive care unit
Immunocompetent	a person who has normal immune responses
Immunocompromised	a person who has impaired immunity due to disease (eg cancer) or treatment (eg corticosteroid drugs or radiotherapy)
Impermeable	does not allow the passage of fluids or solutes, eg bacteria may be impermeable to an antimicrobial agent so that it cannot get into the bacteria

Incidence	the number of episodes of a disease that occur in a specified period of time in a specified group of people, eg the number of infections in people admitted to a hospital or in people undergoing a particular procedure in a given time
Inflammation	the response of tissues to damage caused by physical, chemical or biological agents
Inherent resistance	resistance to an antimicrobial agent that is due to the basic nature of the organism, eg all gram-negative bacteria are impermeable to glycopeptides and are therefore resistant to them
Interferons	a group of chemicals produced by mammalian cells that increase their resistance to viral infection
In vitro	tests undertaken in laboratory equipment, eg test tubes and not in a living human or animal
In vivo	tests undertaken within a living human or animal
IT	information technology such as computers
Local Health Care Group	the equivalent in Wales of Primary Health Care Groups
Meningitis	inflammation of the membranes (meninges) that envelope the brain and spinal cord. Bacteria that cause meningitis include *Neisseria meningitidis*
Meta-analysis	statistical analysis that combines results from several studies to obtain an overall estimate, eg the effectiveness of antibacterial agents to treat acute otitis media
MIC (minimum inhibitory concentration)	the lowest concentration of an antimicrobial agent that can inhibit the growth of a micro-organism. A micro-organism with a low MIC is susceptible to that antimicrobial agent, one with a high MIC is resistant
Micro-organism	any organism that is too small to be visible to the naked eye, eg bacteria, fungi, viruses and protozoa
Monotherapy	treating an infectious disease with one antimicrobial agent
Morbidity	the state of having a disease
Mortality	death
Multi-resistance	a micro-organism that is resistant to two or more unrelated antimicrobial agents
Mutation	a change in the genetic material of an organism, or the resultant change this causes in a characteristic of the individual, caused by an alteration to the nucleic acid structure
Myocardial infarction	sudden loss of the blood supply to the heart muscle (myocardium) followed by death of the muscle. Popularly known as 'heart attack'
Neutropenia	a reduction in the number of white cells in the blood, because of disease or treatment, that renders patients more susceptible to infections
NICE (National Institute for Clinical Excellence)	a new national institute that will give coherence and prominence to information about clinical effectiveness and cost-effectiveness
Normal bacterial flora	the bacteria that normally live on and in the skin, gut, mouth and upper respiratory tract of humans. Also called commensal organisms, they do not normally cause disease, and provide some protection from infection. When antimicrobial agents are used to treat infectious disease they can affect the normal bacterial flora and their ability to provide protection from infection
Opportunist pathogen	a pathogen that infects immunocompromised people but rarely infects immunocompetent people
Optimum duration	the best duration of treatment, not too long or too short
Parenteral	giving drugs by intramuscular or intravenous injection
Pathogen	a micro-organism capable of causing disease

PHLS	Public Health Laboratory Service. An organisation of public health laboratories based in district general and teaching hospitals in England and Wales, and a central facility at Colindale in North London which houses the headquarters, national Reference Laboratories and Communicable Disease Surveillance Centre. Its purpose is to protect the population from infection
Plasmid	a piece of genetic material (DNA) often found in bacteria that is independent of the chromosome
Prevalence	the number of instances of a particular disease or other condition at a particular time, eg the number of people with tuberculosis, or the number infected with a pathogen resistant to antimicrobial agents
Primary Health Care Groups	group of GPs in England who will be responsible for commissioning health services for their populations or patients
Prophylaxis (or chemoprophylaxis)	using an antimicrobial agent to prevent infection, eg giving antimicrobial agents before gut surgery in order to prevent micro-organisms in the gut spreading into the abdomen and producing peritonitis
Protozoan	a single-celled micro-organism, that is more complex and usually bigger than a bacterium and may be free living or parasitic
Quality issues	issues about the quality of health services delivered to patients in hospitals and the community
Randomised control studies	an experimental method for comparing different treatments by randomly assigning people to groups which receive different treatments and comparing outcomes, eg how many people in each group were cured or improved by each treatment
Reactivation	restore to a state of activity. Certain viruses, eg herpes simplex virus, produce recurrent episodes of disease such as cold sores, or genital infection. The virus survives in nervous tissue between episodes of disease and can be reactivated to produce disease
Reference laboratory	a laboratory that carries out more specialised tests on samples received from other laboratories and is usually involved in research relating to its particular area of interest
Replication	the process of making an exact copy of a molecule or an organism
Resistance	the ability of a micro-organism to withstand an antimicrobial agent. See also acquired resistance, multi-resistance and inherent resistance
Respiratory tract infection (RTI)	infection of the respiratory tract including upper respiratory tract infections such as colds, sinusitis, and lower respiratory tract infections such as pneumonia
Reverse transcriptase	an enzyme that makes a DNAcopy of an RNA molecule, and is essential in the replication of viruses such as HIV that use RNAas their genetic material
Ribosome	a particle, consisting of RNA and protein, that occurs in cells and is the site of protein synthesis in the cell
RNA(ribonucleic acid)	one of the two types of nucleic acid in organisms. RNAis a chemical messenger in all organisms and some viruses, eg influenza and HIV, use RNAto carry their genetic information
Selection pressure	environmental conditions that favour the survival and replication of certain individuals, eg the presence of an antimicrobial agent favours the survival of micro-organisms that are resistant to it
Sensitive	organisms that are unable to replicate or are killed by an antimicrobial agent
Septicaemia	severe general infection caused by pathogens and their toxins
Sinusitis	inflammation of the sinuses of the nasal cavities that is commonly caused by infection

Surveillance of disease	the systematic collection and evaluation of data on all aspects of a disease that are relevant to its prevention and control
Tertiary hospital	teaching or specialised hospital that provides specialised care
Topical treatment	drug applied directly, or locally, to the surface of the part being treated, eg the skin or eye
Transmission	passing infectious disease from one person to another or a plasmid from one bacterium to another
Transposon	a piece of DNA(often containing genes for resistance) that can move from one DNA molecule to another
Vaccine	a preparation that can be used to stimulate the development of immunity against one or more pathogens to prevent infections including measles, mumps, polio, rubella, whooping cough, diphtheria, hepatitis A, hepatitis B and rabies
Virulence	the ability of a pathogen to cause disease
Virus	a very small micro-organism that can only survive and multiply within a living host cell
Zoonosis	an infectious disease of animals that can be transmitted to humans, eg brucellosis and rabies

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