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 USAand 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.

12.7 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

12.8 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

MRSAare 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 USAthe 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.

13 PREVENTING THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

KEY POINTS

Without a guarantee of new antimicrobial agents, conservation of present agents is desirable

Careful antimicrobial use should slow the emergence of new resistance

Reduced use *may* – but cannot be guaranteed to – reduce present resistance

Prevention of spread of resistant strains is also critical, especially for MRSA

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.*

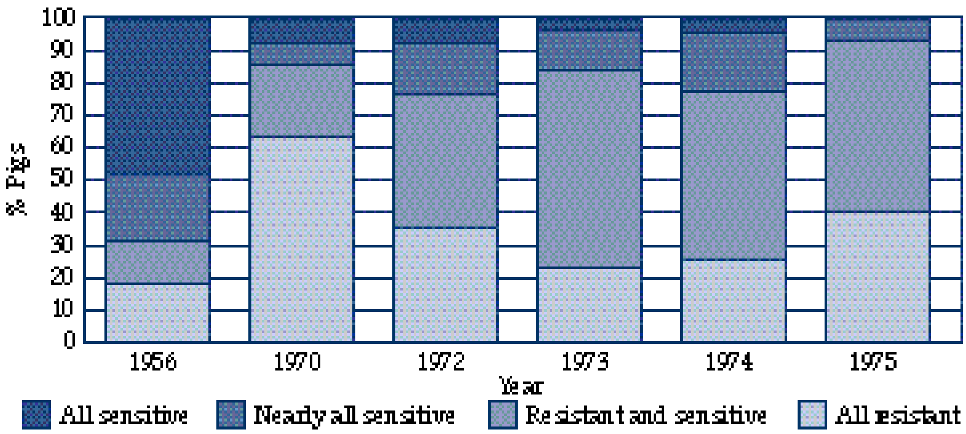
The slow rate at which resistance clears from populations is further illustrated by the work of Smith [231] who examined the incidence of tetracycline-resistant *Escherichia coli* in pigs in the years immediately after 1971, when its use as a growth promoter was prohibited. His results are summarised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

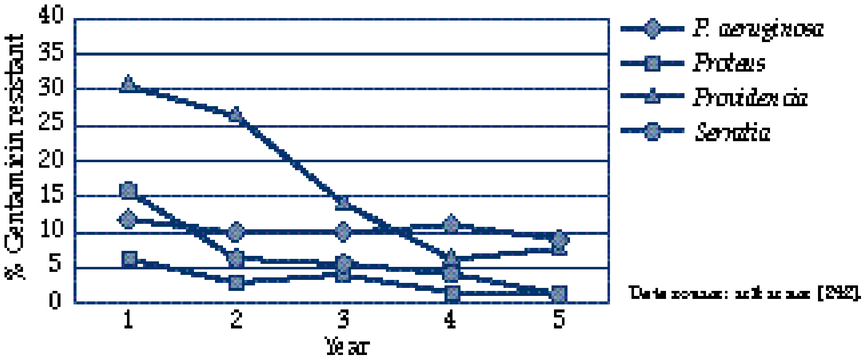
A final study, and one of the most optimistic, is by Betts *et al* [242], who examined trends in aminoglycoside resistance at a university hospital after substitution of amikacin for gentamicin as the first-line aminoglycoside in empirical therapy. Rates of gentamicin resistance fell across a range of 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 USAand 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

KEY POINTS

We need:

Guidelines for therapy of common infections

Computer-assisted antimicrobial prescribing

Education of prescribers, health care staff and consumers to improve awareness of antimicrobial resistance

Faster diagnosis to identify patients needing antimicrobial therapy

Faster susceptibility testing to allow better-tailored therapy

Better surveillance of antimicrobial resistance

Better communication of surveillance data

Better control of infection to stop the spread of resistant bacteria

A higher profile for research on the epidemiology and bases of resistance

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.

16 PROMOTING BETTER PRESCRIBING

KEY POINTS

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.

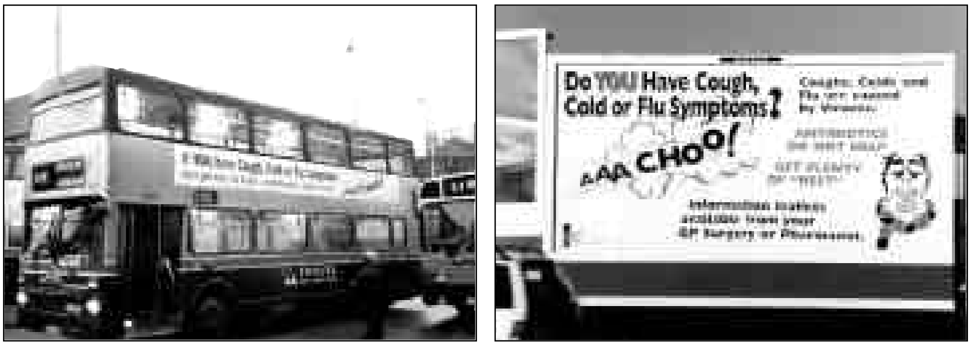
Various ways of communicating these messages could be envisaged, from simple slogan-based advertising:

"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).

FIGURE 15

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.

FIGURE 16

PATIENT INFORMATION LEAFLET

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

16.4 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'.

17 SURVEILLANCE OF RESISTANCE

KEY POINTS

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.

19 CHANGING PRACTICE

KEY POINTS

Professional changes cannot be achieved in isolation

Changes in public expectations are needed too

Changes need planning and a supportive environment

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.

19.1 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].

19.2 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