

3 LOOKING INTO THE ABYSS

KEY POINTS

- Antibiotics enable huge advances in medicine
- Antibiotic use selects for resistant bacteria
- Resistant bacteria accumulate and spread
- Resistance increases clinical complications, lengthens hospital stay and adds cost
- Development of new antibiotics is slow, expensive and cannot be guaranteed
- With more resistance and few new antimicrobial agents, modern medicine is threatened

For two generations, antimicrobial agents have altered expectations of life and death. The fever hospitals and tuberculosis sanatoria have gone. In the early 1930s, deaths from sepsis after childbirth in the UK were 100–120 per 100,000 births; after antibiotics were introduced this rate fell to almost zero. Antimicrobials have enabled operations and treatments such as transplantation to be undertaken that were previously unthinkable because they exposed the patient to a huge infection risk.

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

Until recently, man kept ahead and new antimicrobials were developed faster than bacteria developed resistance. Gradually, though, a change occurred: while the 1950s and 60s saw the discovery of numerous *new classes* of antimicrobials, the 1980s and 90s yielded only relative improvements *within* classes. Now, in the closing years of the century, micro-organisms are 'getting ahead', and therapeutic options are narrowing.

In the UK there are bacteria resistant to many antimicrobials. Elsewhere the situation is often worse. In Japan, strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa* are resistant to all established antimicrobials. There is every reason to fear that such pathogens will be imported to the UK, or will evolve independently here.

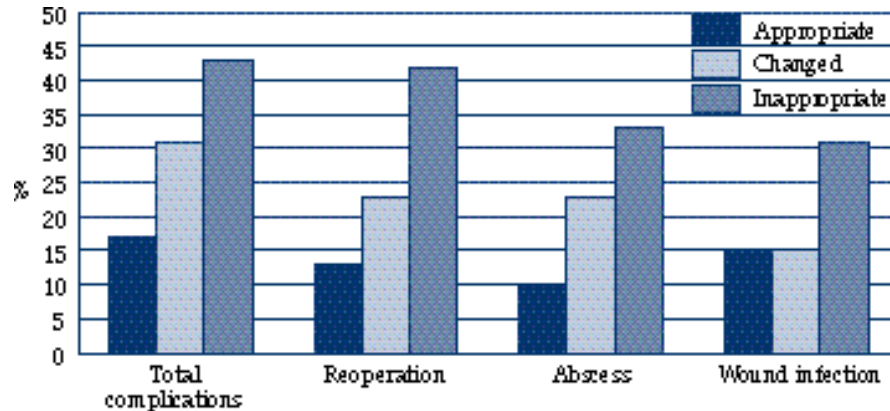
The spread of resistance threatens a return to darker times, when surgery was restricted to simple operations on the otherwise healthy, and when organ

transplants, joint replacements and immunosuppressive therapies were unthinkable.

Even when resistance does not prevent effective therapy, it adds cost. The initial antimicrobials must be replaced with agents that are more expensive or have undesirable side-effects. More generally, patients whose therapy proves inappropriate as a result of resistance are more likely to experience complications .

In one study, reoperation, abscess formation and wound infection were all commoner in those surgical patients who received inappropriate therapy.

Figure 2 Complications (%) after appropriate and inappropriate therapy in surgical peritonitis



The threats to health posed by antimicrobial resistance are:

- **Some conditions may become untreatable**
- **Empirical treatment may be inappropriate and time may be lost in critically ill patients**
- **Length of hospital stay, antimicrobial use, morbidity, mortality and costs may be increased**
- **More toxic, less effective or more expensive alternative drugs may have to be used.**

4 ANTIMICROBIAL AGENTS

The range of antimicrobial agents available and their activities are summarised in this section of the main Report, to which the reader is referred.

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

KEY POINTS

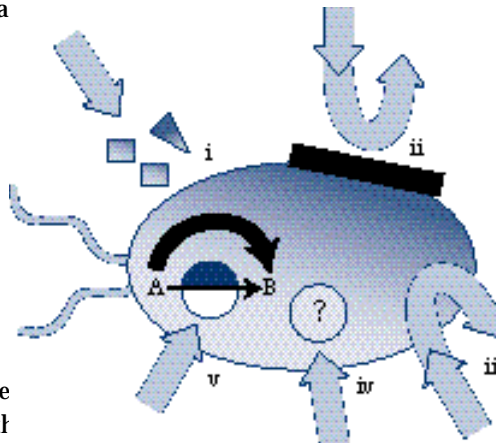
- Darwinian selection
- Antimicrobial agents kill sensitive organisms, resistant ones survive
- Sensitive organisms may become resistant by mutation
- Resistances can transfer among different organisms
- Some species are inherently resistant and are selected by antimicrobial agents
- Bacteria accumulate multiple resistances to unrelated antibiotics

The great principle of antimicrobial resistance is 'Survival of the Fittest'. Antimicrobials kill susceptible bacteria but resistant ones survive to infect other patients. At the same time, advances in medicine enlarge the pool of patients susceptible to infection by organisms that historically were harmless, but which are adept at developing resistance.

Resistance can arise via mutation, gene transfer or by the selection of inherently resistant species. The importance of these processes varies with the organism, the antimicrobial agent and the clinical setting.

Figure 3 Mechanisms of antimicrobial resistance

The antimicrobial, drawn as a bullet, heads towards its target. Resistance may arise (i) if it is inactivated before it reaches the target, (ii) if the bacterial cell becomes impermeable, (iii) if the cell becomes able to pump the antibiotic back out, (iv) if the target is altered so that it no longer recognises the antimicrobial, or (v) if the bacterium acquires an alternative metabolic pathway, by-passing the site of action.



BOX 3. MULTI-RESISTANCE

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

6 DOES USE OF ANTIMICROBIAL AGENTS CAUSE RESISTANCE?

KEY POINTS

- Resistance has repeatedly emerged to new drugs after clinical use
- Most resistance occurs in countries and units where use is heaviest
- Resistance may be selected in the target organism during therapy
- Resistant commensal body flora may also emerge during therapy
- Evidence linking antimicrobial use in man and resistance is clear and overwhelming, but mostly circumstantial

Key facts are:

- Acquired resistance is absent from bacteria ante-dating the antimicrobial era. The only resistances seen are those inherent to particular species.*
- Introduction of new antimicrobials has been followed repeatedly by resistance. The time scale has varied, reflecting the complexity of the evolution, but the pattern is constant.*
- Resistance often develops in the normal bacterial flora of individuals receiving antimicrobial therapy. If a further infection arises from this flora, it is more likely to be resistant than in patients who have not received prior therapy.*
- Resistance is greatest in countries and hospital units where antimicrobial use is heaviest. The clearest example is the excess of resistance in intensive care units*

KEY POINTS

- In many common infections the decision to prescribe is finely balanced
- Infections are often viral and unaffected by antibiotics
- Decisions to prescribe are influenced by patients' expectations
- Patients believe that antimicrobials will work for them
- Unnecessary or marginal use exacerbates the selection of resistance
- Reducing unnecessary antibiotic use must involve health care workers, patients and the pharmaceutical industry

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

The unnecessary prescription and consumption of antimicrobials is everyone's responsibility. Effective treatment of infectious disease can only be preserved through a determination on the part of policy makers, manufacturers, prescribers and consumers to minimise unnecessary consumption. There may be difficult clinical decisions, as exemplified in Boxes 5-8, but there are also circumstances when prescription of an antimicrobial is clearly wrong. A patient with a common cold should not receive an antibiotic and women with uncomplicated cystitis should not receive antibiotics for more than three days.

BOX 4. THE ANTIMICROBIAL TUG OF WAR

What stimulates prescribing ?

Prescribers

Failing to prescribe may lead to clinical complications or litigation
Applying rules learned as a student which may no longer be appropriate
'Clinical judgement'
Scientific and promotional literature
A prescription is an easy way to end a consultation

Patients

Patients' expectations drive prescribing
Many patients expect a 'script'
Belief that they need an antibiotic to stop a cold 'going to their chest'
Anxiety over sick children

Nurses

May not fully appreciate the risks associated with inappropriate use of antimicrobials

Pharmacists

Often first community contact; may advise that a prescription is necessary

Pharmaceutical industry

Wants to sell its products

What inhibits prescribing ?

Prescribers

Advice from specialists in microbiology and infectious disease, who discourage excessive prescribing
Good basic training on risks and benefits of antimicrobial treatment

Patients

Some patients are averse to prescription, and seek reassurance that they will recover without an antibiotic

Nurses

See the problems associated with over-prescription – resistance, ward-closures, antibiotic-associated diarrhoea – and try to educate prescribing colleagues and patients

Pharmacists

Particularly in hospitals, have an important role in controlling prescribing and identifying inappropriate prescribing

Pharmaceutical industry

Wants to ensure long product life

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

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

BOX 5. THE PAINFUL EAR

Acute otitis media (AOM – infection of the middle ear) is common in childhood. A child with AOM is distressed, unhappy and febrile. The parents are concerned and eager for the GP to act. The GP may feel under pressure to prescribe. It is easy to write the prescription and see the family leave satisfied. When the symptoms improve this is attributed to the antibiotic, reinforcing the cycle of expectation. A GP will see many children with AOM each year and most will receive an antibiotic.

Reviews on AOM suggest that the benefit of routine antimicrobial use is unproved or modest. A proportion of children do benefit but it is difficult to predict which ones. Countries with lower rates of antibiotic prescribing for AOM **do not** have any increase in the number of complications compared with those where a prescription is usual. Even if antibiotics are prescribed, there is debate about the appropriate length of treatment: three and ten day courses were equally effective in one study.

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

BOX 6. THE SORE THROAT

Sore throats are common, particularly in children. Most are viral and can be left to run their course without antibiotics. Indeed, recurrence and relapse may be more common in those who have had early treatment with antibiotics.

Nevertheless, the GP can come under considerable pressure to prescribe an antibiotic for a sore throat. A recent study showed that patients with sore throats were more likely to leave the consultation satisfied if they received a prescription. However, they were no more likely to be satisfied at the end of the illness. Those who received antibiotics were more likely to return for treatment in future attacks and were more likely to believe in the efficacy of antibiotics.

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

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

BOX 7 SINUSITIS

Several studies, including randomised controlled trials, have shown antibiotics to be effective in proven acute sinusitis. Most of these studies have used ten day courses of antibiotics. One comparative study showed that three days of antibiotics were as effective as ten days.

Recent overviews of the treatment of acute sinusitis-like symptoms in adults in the primary care setting suggest that there is no benefit from antibiotic treatment.

The adult with 'sinusitis-like symptoms' in primary care does not need immediate antibiotics.

In proven acute sinusitis three days of antibiotics are as effective as ten.

BOX 8 CYSTITIS

Each year about one woman in 20 will present to her GP with symptoms of cystitis; about half of these women will have an infection (defined by the presence of a significant number of bacteria in the urine). Most of these infections in otherwise healthy women are caused by coliform bacteria.

Uncomplicated cystitis can be treated empirically with trimethoprim. If resistance is common locally, the medical microbiologist can advise on an appropriate alternative. Several studies have shown that a three day course of treatment is as effective as a five or seven day course.

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

8 WHERE ARE ANTIMICROBIAL AGENTS USED?

KEY POINTS

- 50% of antibiotic use in the UK is in man, 50% in animals
- 80% of human use is in the community
- 50% of community use is in respiratory tract infection, 15% in urinary tract infection
- Considerable local and regional variation exists in levels of community prescribing
- In hospitals, antimicrobial agents account for 10–30% of the drugs budget

COMMUNITY PRESCRIBING

About 50 million prescriptions for antibiotics are dispensed in England every year – an average of one prescription per person per year. Most human antibiotic prescribing in the UK (80%) is of oral antibiotics in the community. About half of this community use is in respiratory tract infection (RTI), with a further one-sixth in urinary tract infection (UTI). Most community antimicrobial prescribing is by GPs, but dentists account for about 7%. Usage is subject to approximately two-fold variation between Districts with the lowest and highest prescribing, with no obvious explanation.

PRESCRIBING IN HOSPITALS

Although hospital prescribing accounts for only 20% of human usage, it is of key importance because it is concentrated in a small population brought together in a confined environment. Also hospitals – with high populations of immunocompromised patients – are fertile breeding grounds for opportunist bacteria that are adept at accumulating resistance.

Audits at a teaching hospital trust showed that 20–25% of patients had received an antibiotic within the previous 24 h, with a range from 40 to 50% in ICU to less than 10% in ENT surgery. As in the community, most prescribing is for RTI.

Figure 4 Hospital and community use of some antimicrobial agents

ANTIMICROBIAL AGENTS	RETAIL (COMMUNITY) (kg)	HOSPITAL (kg)
Total Systemic Antibiotics	385600	80900
Broad – spectrum penicillins	160406	25556
Med/narrow-spectrum penicillin	59800	17200
Tetracyclines + combinations	45900	1600
Cephalosporins + combinations	35900	15100
Trimethoprim combinations	10900	3500
Fluoroquinolones	10300	3600
Nitrofurantoin	742	45
Nalidixic acid	588	59
Fusidic acid	354	454
Aminoglycosides	109	5300
Chloramphenicol + combinations	25	88
Rifampicin/rifamycin	12	14
Other β -lactams	9	527
Glycopeptides	9	493

Data kindly provided by IMS Health UK, Maxims Database

Figure 5 The pyramids of antimicrobial use and selection for antimicrobial resistance



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

9 THE EXTENT OF BACTERIAL RESISTANCE IN THE UK

	Penicillins	Cephalosporins	Carbapenems	Tetracycline	Chloram-phenicol	Aminoglycosides	Quinolones	Trimethoprim	Fusidic acid	Erythromycin	Glycopeptides	Rifampicin	Ethambutol & isoniazid
<i>S. aureus</i> MethS	●	○	○	★	★	★	★	★	★!	●	○	★!	-
MRSA	●	●	●	★	●	●	●	●	★!	●	○	★!	-
Enterococci	★	-	★	●	●	●	-	●	-	●	★	-	-
-haem. streps	○	○	○	★	★	-	-	★	-	★	○	★	-
<i>S. pneumoniae</i>	★	★	○	★	★	-	-	-	-	★	○	★!	-
Viridans streps	★	★	○	★	★	●	-	●	-	★	○	★!	-
<i>E. coli</i>	●	★	○	●	●	★	★	●	-	-	-	-	-
<i>Klebsiella</i> spp	-	★	○	●	●	★	★	●	-	-	-	-	-
<i>Enterobacter</i>	●	●!	○	●	●	★	★	●	-	-	-	-	-
<i>Pseudomonas</i>	★!	★!	★!	-	-	★!	★!	-	-	-	-	-	-
<i>Acinetobacter</i>	●	●	★	●	●	●	★	-	-	-	-	-	-
<i>N. meningitidis</i>	○	○	○	○	●	-	○	★	-	-	-	★	-
<i>N. gonorrhoeae</i>	★	○	○	★	○	-	★	★	-	★	-	★	-
<i>H. influenzae</i>	★	★	★	★	★	-	★	★	-	-	-	-	-
<i>M. tuberculosis</i>	-	-	-	-	-	-	-	-	-	-	-	★	★

- Inherently resistant.
- ★ Acquired resistance in <20% of isolates.
- Acquired resistance in >20% of isolates.
- Acquired resistance unknown, or virtually so.
- ! Resistance emerges readily by mutation.

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

10 CURRENT RESISTANCE PROBLEMS IN THE UK AND WORLD-WIDE

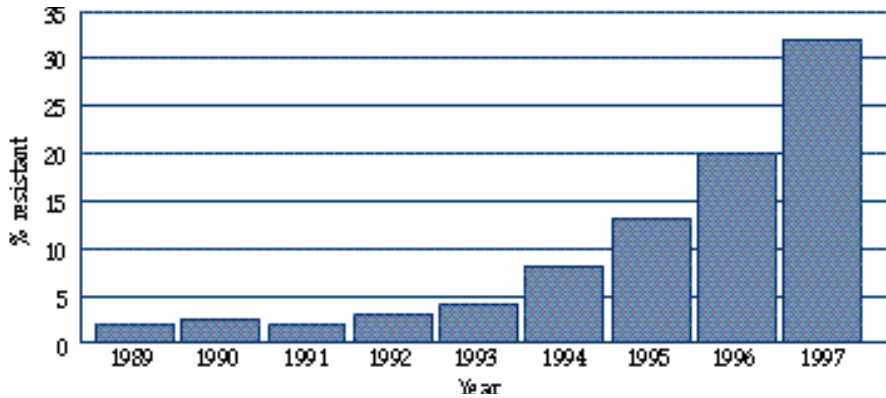
KEY POINTS

- Resistance is accumulating world-wide in many bacteria
- The UK situation is not as bad as that in many countries, but the trend is to more resistance
- A major problem in the UK is methicillin-resistant *Staphylococcus aureus* (MRSA)
- Other major problems include pneumococci, enterococci and hospital gram-negative opportunists
- Resistance is emerging in viruses and fungi

STAPHYLOCOCCUS AUREUS

When penicillin was introduced in 1944, over 95% of *Staphylococcus aureus* isolates were susceptible, but this proportion has since shrunk to 10%. The introduction of β -lactamase-stable penicillins (e.g. methicillin and flucloxacillin) in the early 1960s was swiftly followed by the emergence of the first methicillin-resistant *Staphylococcus aureus* (MRSA). Subsequently, a series of epidemic MRSA (EMRSA) strains have evolved and spread, some locally, others internationally. Many are resistant to a number of antibiotics, with only glycopeptides (vancomycin and teicoplanin) remaining active. Recently there have been reports of MRSA with intermediate resistance to vancomycin and teicoplanin. These are resistant to all available antimicrobials and, unlike other organisms where pan-resistance is seen, have considerable pathogenicity for those not severely immunocompromised.

Figure 6 Proportion (%) of *Staphylococcus aureus* isolates from blood and CSF that were resistant to methicillin, 1989–97

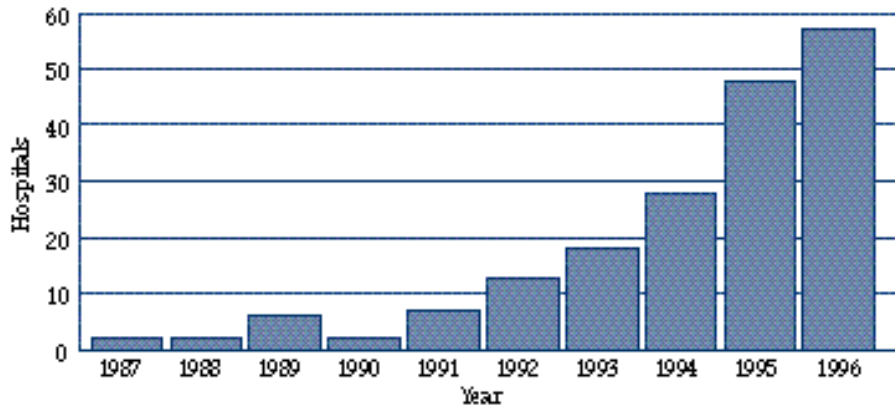


ENTEROCOCCI

Enterococci are a part of the normal human gut flora, where they are harmless. They have little virulence but can cause infection in patients whose health is impaired, particularly in specialised hospital settings (eg renal dialysis and bone marrow transplant units). Serious infections are extremely difficult to treat because of resistance.

Enterococci are intrinsically resistant to quinolones and cephalosporins and clinical use of these agents may explain the rising importance of enterococci. In addition, enterococci readily gain resistance to other antimicrobials. Recent concern has centred on the emergence and spread of enterococci with resistance to the glycopeptides (vancomycin and teicoplanin) (Figure 7). Many glycopeptide-resistant enterococci (GRE) are resistant to *all* established antimicrobials, forcing clinicians to use untested agents or combinations with no guarantee of success.

Figure 7 Number of hospitals submitting enterococci resistant to glycopeptides to the PHLS Antibiotic Reference Unit: England and Wales, 1987–96



STREPTOCOCCUS PNEUMONIAE

Streptococcus pneumoniae is most important as a cause of community-acquired pneumonia, which may lead to bacteraemia. It is also a frequent cause of otitis media and is one of the commonest causes of bacterial meningitis. Historically, *Streptococcus pneumoniae* was exquisitely susceptible to penicillin, which could be used in most pneumococcal infections, including meningitis. Macrolides (eg erythromycin), tetracyclines and co-trimoxazole were alternatives in respiratory tract infection, whereas several cephalosporins and meropenem were – and are – alternatives in meningitis. Pneumococci with low-level penicillin resistance were recorded in the late 1960s and some with high-level resistance began to be seen in the late 1970s. These are now increasing, both in frequency and in the level of their resistance (Figure 8). There is also concern about the risk of importation of resistant strains from those countries (eg Spain) where the rate of resistance is much higher.

Figure 8 Prevalence of resistance in pneumococci from blood and CSF in England and Wales, 1989–95.

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

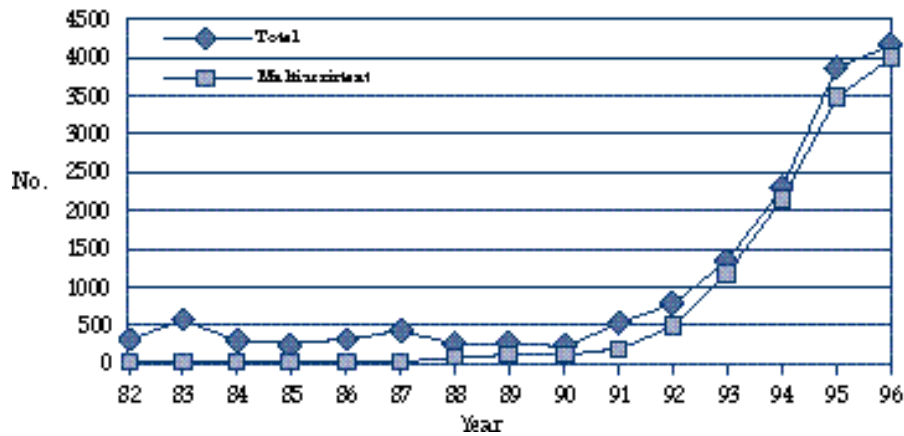
HOSPITAL-ACQUIRED GRAM-NEGATIVE OPPORTUNISTS

Many different gram-negative bacteria can cause opportunistic infection in immunocompromised patients. The organisms most often involved include members of the genera *Escherichia*, *Klebsiella*, *Proteus*, *Enterobacter* and *Acinetobacter*. *Escherichia coli* is also the commonest cause of cystitis in the community. Resistance to many antibiotics is increasing in these pathogens, notably to cephalosporins, quinolones and trimethoprim.

ENTERIC PATHOGENS – SALMONELLA

Several bacterial genera are important in food poisoning. At present multiple drug resistance is a major problem in *Salmonella*, particularly *Salmonella typhimurium*, where an important recent factor was epidemic spread of multi-resistant *Salmonella typhimurium* DT 104 in bovines and its increasing recovery from man.

Figure 9 Isolation of *Salmonella typhimurium* DT 104 from man, 1982–96



CAMPYLOBACTER SPECIES

These organisms, which are the commonest cause of bacterial gastrointestinal infection, can cause severe food poisoning requiring antibiotic treatment. Macrolides and ciprofloxacin are used. Emerging resistance to ciprofloxacin is a concern.

NEISSERIA GONORRHOEAE

Sulphonamides were effective against gonorrhoea on introduction in 1937 and almost invariably ineffective by 1944. Penicillin resistance was slower to emerge, but the agent's activity has been gradually eroded, with higher doses being needed. Strains that produce β -lactamases (penicillin-degrading enzymes) were first detected in gonococci from the Far East and from West Africa. These penicillin-destroying strains are rare in the UK.

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

NEISSERIA MENINGITIDIS

This organism is the commonest cause of bacterial meningitis. Frank penicillin resistance is not yet a problem, but the proportion of isolates with decreased susceptibility increased from <1% in 1985/6 to 14% in 1995/6.

MYCOBACTERIUM TUBERCULOSIS

Tuberculosis (TB) remains the commonest bacterial cause of morbidity and mortality world-wide, with nearly 8 million new cases and 3 million deaths annually, mostly in developing countries. A steady decline in clinical cases in the developed world ceased or reversed in the mid-1980s.

Tuberculosis is treated with combinations of three or four agents for at least 6 months. Monotherapy leads rapidly to resistance by selecting spontaneous mutants. Even with combination therapy, resistance emerges when there is poor concordance by the patient, incorrect dosage or malabsorption of the drugs.

Resistance is a major problem in many developing countries and may be imported into the UK.

FUNGAL INFECTION

Fungal infections are assuming a greater importance, largely because of their increasing incidence in patients with AIDS, transplant recipients, neutropenic cancer patients and debilitated intensive care patients. In the 1980s there was an 11-fold rise in the incidence of disseminated candidosis among patients admitted to hospitals in the USA.

The rise in the number of serious fungal infections has resulted in an increase in the use of antifungal agents. This has contributed to the emergence of resistance to a number of important compounds. In recent years, resistance to azole antifungals (eg fluconazole) has become a significant problem in several groups of patients, particularly those with AIDS.

Resistance has been documented to virtually all the antiviral drugs available in the UK. Resistance generally accrues by step-wise mutation, and often leads to a virus with reduced susceptibility rather than one with frank clinical resistance.

Combination therapy may militate against the development of resistance in HIV, but the risk cannot be discounted.

What next for antimicrobial resistance ?

FIRST, it seems inevitable that vancomycin-intermediate MRSA will spread. Worse, gene exchange occurs between staphylococci and enterococci and it is likely that the high-level glycopeptide resistance of enterococci will spread to MRSA. Its spread to pneumococci is also possible. The consequences would be severe: glycopeptides are the drugs of last resort against many serious gram-positive pathogens (eg resistant pneumococci in meningitis).

SECOND, it is also common to see gram-negative bacteria susceptible only to the carbapenems, imipenem and meropenem. Unfortunately, carbapenem resistance is now seen increasingly in hospital opportunists such as *Pseudomonas aeruginosa* and *Acinetobacter*.

OTHER RESISTANCES to be feared include those in species that have, thus far, remained remarkably susceptible. Obvious risks are penicillin resistance in *Neisseria meningitidis* and *Streptococcus pyogenes*.

Penicillin resistance in *Streptococcus pyogenes* is remarkable by its continued absence. This species, once the most feared of hospital wound pathogens, has remained exquisitely sensitive to penicillin since the 1940s. Nevertheless, gene exchange occurs between *Streptococcus pyogenes* and staphylococci and there is a risk that β -lactamase production may spread from the latter to the former.

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