

CURRENT RESISTANCE PROBLEMS IN THE UK AND WORLD-WIDE

KEY POINTS

Resistance is accumulating world-wide in many bacterial species

The UK situation is not as bad as that in many countries, but the trend is to more resistance

A major problem in UK is methicillin-resistant *Staphylococcus aureus* (MRSA)

Other major problem species include *Streptococcus pneumoniae*, enterococci and many hospital-acquired gram-negative opportunists

Resistance is emerging in viruses and fungi, as well as bacteria

10.1

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

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

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

When penicillin was introduced in 1944 over 95% of *Staphylococcus aureus* isolates were susceptible, but this proportion has since shrunk to 10%. In the 1950s, isolates resistant to penicillin and tetracycline became a major hospital problem. The introduction of β -lactamase-stable penicillins (eg methicillin, flucloxacillin) in the early 1960s overcame this problem, but was swiftly followed by the emergence of the first MRSA. These MRSA did not rapidly become prevalent, perhaps because another effective antimicrobial – gentamicin – entered use. However, by the late 1970s, gentamicin-resistant MRSA had emerged; subsequently a series of epidemic MRSA (EMRSA) strains have evolved and spread. These are consistently susceptible only to the glycopeptides, vancomycin and teicoplanin. Many MRSA isolates also appear to be susceptible to fusidic acid, rifampicin and/or (decreasingly) ciprofloxacin, but mutational resistance is prone to emerge if these agents are used for therapy.

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

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

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

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

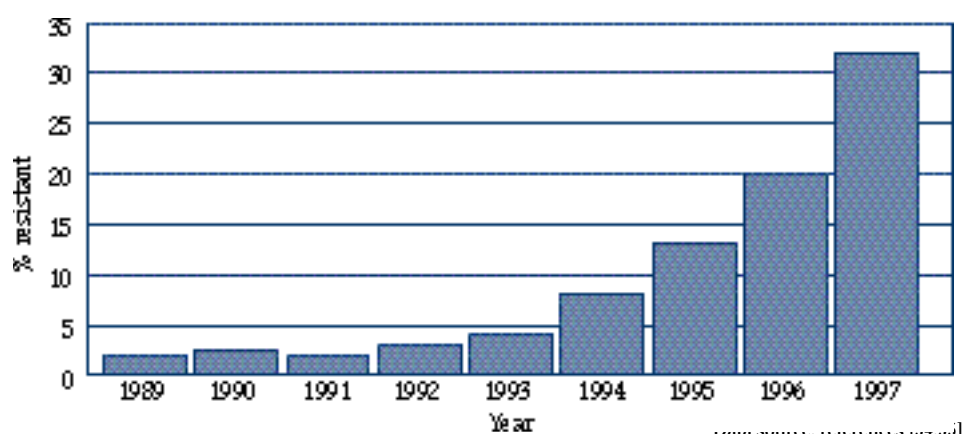
10.1.1 MRSA IN THE UK AND INTERNATIONALLY

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

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

FIGURE 8

PROPORTION (%) OF STAPHYLOCOCCUS AUREUS ISOLATES FROM BLOOD AND CSF THAT WERE RESISTANT TO METHICILLIN, 1989–97



MRSA rates around the world are summarised in Table 7. In general, they are lowest in those countries that have strict control of infection policies and highest in those that have liberal policies. The rates are distorted by the facts that MRSA strains are clonal in origin and that different strains are prevalent in different parts of the world; some of these may be more adept than others at spreading between patients.

TABLE 7

INCIDENCE OF MRSA IN DIFFERENT PARTS OF THE WORLD

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

*MRSA as a percentage of all isolates of *Staphylococcus aureus*.

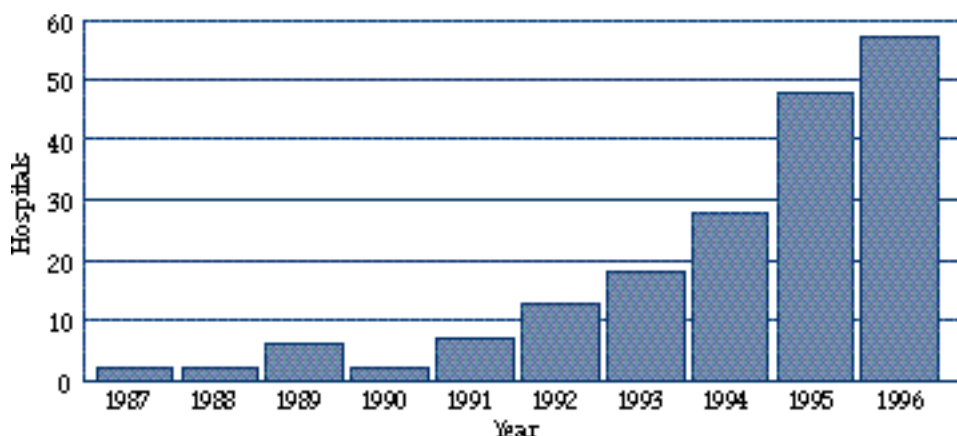
Enterococci are a part of the normal human gut bacterial flora, where they are harmless. They have low virulence but can cause infection in patients whose resistance is impaired, particularly in specialised hospital settings such as renal dialysis and bone marrow transplant units. If they reach normally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

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

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

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

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

FIGURE 9**NUMBER OF HOSPITALS SUBMITTING ENTEROCOCCI RESISTANT TO GLYCOPEPTIDES TO THE PHLS ANTIBIOTIC REFERENCE UNIT: ENGLAND AND WALES, 1987-96**

Data source: PHLS Antibiotic Reference Unit, data on file.

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

10.3***STREPTOCOCCUS PNEUMONIAE***

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

10.3.1 RESISTANCE TO ANTIBACTERIAL AGENTS

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

Streptococcus pneumoniae strains with low-level penicillin resistance were recorded in the late 1960s and those with high-level resistance began to appear in the late 1970s. Strains with low-level resistance still respond to penicillin in respiratory tract infections and bacteraemia, but not in meningitis. Strains with high-level penicillin resistance may still respond to high-dose penicillin in the respiratory tract but, with MICs (minimum inhibitory concentrations – the lowest drug levels to stop the bacteria from growing) of 8 mg/l now being recorded for the most resistant isolates, there is little doubt that the ‘border of the possible’ is close. Strains with high-level penicillin resistance are often barely susceptible to cephalosporins in meningitis, and these drugs may need combination with vancomycin, which penetrates poorly at this site.

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

10.3.2 RESISTANCE IN THE UK

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

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

TABLE 8

PREVALENCE OF RESISTANCE TO ANTIBACTERIAL AGENTS IN STREPTOCOCCUS PNEUMONIAE: ENGLAND AND WALES

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

Data source: reference [60].

TABLE 9

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

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

Data source: reference [60].

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

10.3.3 RESISTANCE IN OTHER COUNTRIES

Although rates of resistance in *Streptococcus pneumoniae* are increasing in the UK, they are lower than in many other countries. This should not encourage complacency: resistance rates comparable to current UK levels applied in France between 1984 and 1987, but thereafter penicillin resistance increased to 20% by 1992. Such swift increases often indicate clonal spread, as illustrated by events in Iceland: until 1988 the rate of penicillin resistance was <1% in Iceland, but it rose to 20% by 1993, reflecting import of resistant strains from Spain by returning holiday-makers, and their dissemination in child-care facilities [62]. Similar dissemination has since occurred in the USA.

FIGURE 10

RESISTANCE TO PENICILLIN IN *STREPTOCOCCUS PNEUMONIAE*: SEVERAL EUROPEAN COUNTRIES

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



Data source: reference [61].

10.4

HOSPITAL-ACQUIRED GRAM-NEGATIVE RODS

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

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

10.4.1 BASIS OF RESISTANCE

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

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

10.4.2 RESISTANCE IN THE UK

Rates of resistance to commonly used anti-gram-negative antimicrobials are summarised in Table 10, which shows data for isolates from blood and CSF specimens in England and Wales between 1989 and 1997, as reported to the PHLS Communicable Disease Surveillance Centre. Except for ampicillin and trimethoprim, most of the agents retained good activity against the major species. Retention of activity by gentamicin, which has been available since 1963, is especially striking.

However, detailed examination reveals several disturbing features:

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

10.4.3 RESISTANCE IN OTHER COUNTRIES

The rates of resistance in gram-negative rods in the UK are low by international standards. Rates are even lower in the Scandinavian countries and the Netherlands, similar to the UK in Germany, Austria and Switzerland, but higher in Southern Europe, much of Asia and the Americas. The highest rates are often in the more prosperous developing countries, eg SE Asia, Turkey and Argentina. Rates of resistance among gram-negative rods in the USA are summarised in Table 11 for comparison with Table 10, which shows UK data. The low rates of gentamicin resistance in the UK have been remarked already; they are two to three-fold lower than those for the USA in the same period. Also, rates of resistance to ciprofloxacin and ceftazidime among the UK isolates mostly compare favourably with those in the USA, which, themselves, are below those in countries where use of antimicrobial agents is unrestricted. At one extreme, it is common to see 20–40% resistance to gentamicin in gram-negative rods isolated from patients in tertiary hospitals in Southern Europe, Japan and the Americas. A 1992 survey found that 70% of the *Enterobacter* isolates from Athens hospitals were resistant to cefotaxime and ceftazidime [64], and up to 60% of *Escherichia coli* are resistant to ciprofloxacin in India. Greece has long had a reputation for high rates of resistance. In the case of India, multiple 'pirated' brands of ciprofloxacin are available over-the-counter, some of low potency and all (owing to cost) prone to be under-dosed.

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

TABLE 10

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

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

Data source: reference [65].

TABLE 11

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

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

10.5

ENTERIC PATHOGENS

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

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

10.5.1 SALMONELLAE

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

TABLE 12

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

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

n = number of isolates tested.

Data source: PHLS

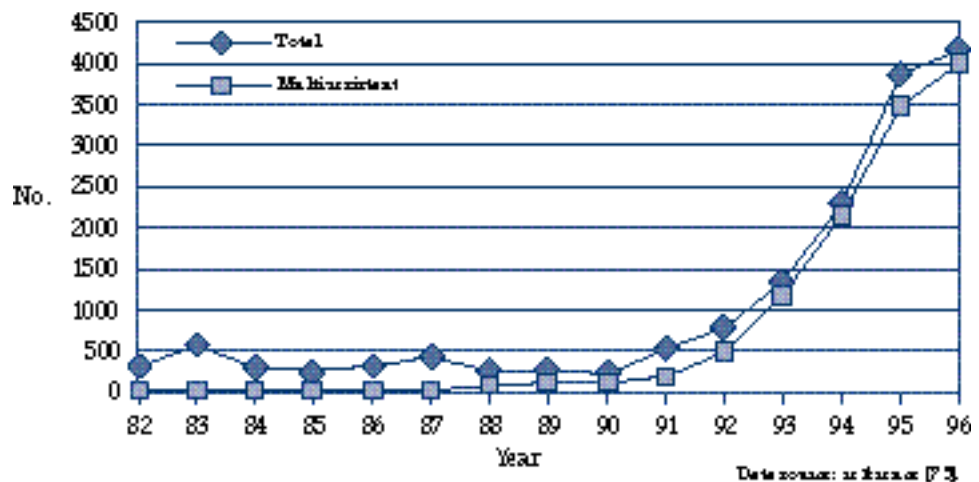
Most resistance is concentrated in *Salmonella typhimurium* (Table 12), and, since the 1960s there has been a series of epidemics of this serotype (caused by different phage types), with increasing resistance. From 1964 to 1968 there was an extensive epidemic of multi-resistant *Salmonella typhimurium* DT 29 in bovines and humans in the UK. As a result of this epidemic and of wider concern, the Swann Committee recommended that certain antibacterial agents should be available only on prescription for veterinary use and should not be used for growth promotion [66] (Section 12.12). Legislation followed and by 1970 type DT 29 was rare in bovines. For the next 6 years only about 8% of salmonellae from cattle and 3% from humans were multi-resistant [67]. However, from 1975 to the mid-1980s there was a substantial upsurge in the incidence of multi-resistant *Salmonella typhimurium* from food animals, particularly bovines, and an increase in multi-resistant isolates from humans. Phage types DT 204, 193 and 204c predominated [68]. A feature of this period was sequential acquisition of plasmids and transposons coding for resistance to multiple antibacterial agents. This followed the introduction and use (as therapeutic agents, not growth promoters), in calf husbandry, of new antibacterial agents – notably apramycin, a gentamicin analogue [69,70]. By the end of 1990, 60% of *Salmonella* isolates from cattle were multi-resistant [71].

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

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

FIGURE 11

RESISTANCE TO ANTIBACTERIAL AGENTS OF *SALMONELLA* TYPHIMURIUM DT 104 ISOLATED FROM MAN: ENGLAND AND WALES, 1982-96



10.5.2 *CAMPYLOBACTER* SPP

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

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

TABLE 13

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

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

Data source: PHLS data.

10.5.3 OTHER ENTERIC PATHOGENS

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

10.6

NEISSERIA GONORRHOEAE

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

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

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

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

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

10.6.1 RESISTANCE IN THE UK

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

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

TABLE 14

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

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

* += PPNG.

Data source: PHLS Gonococcal Reference Unit.

TABLE 15

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

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

* += PPNG.

Data source: PHLS Gonococcal Reference Unit.

10.7

NEISSERIA MENINGITIDIS

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

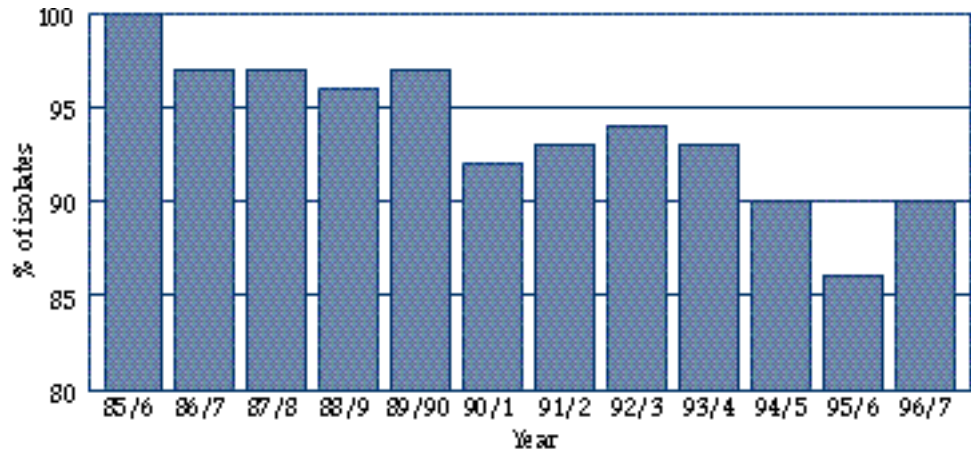
10.7.1 RESISTANCE IN THE UK

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

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

FIGURE 12

PROPORTION OF CLINICAL *NEISSERIA MENINGITIDIS* ISOLATES HIGHLY SENSITIVE TO PENICILLIN (MIC <0.1 mg/l)



Data source: PHLS Submission to House of Lords enquiry.

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

10.8

MYCOBACTERIUM TUBERCULOSIS

Tuberculosis (TB) remains the commonest bacterial cause of death from any single infectious agent in adults world-wide, with an estimated 8 million new cases and 3 million deaths annually, mostly in the developing world. A steady decline in clinical cases in the developed world, and some parts of the developing world, ceased or reversed in the mid-1980s. There have been several contributing factors:

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

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

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

10.8.1 RESISTANCE IN ENGLAND AND WALES

A review was carried out of *Mycobacterium tuberculosis* isolates submitted to the PHLS from residents of England and Wales between 1982 and 1991 [88]. Overall, 6.1% of 'initial isolates' (ie first isolates from newly diagnosed patients) were resistant to isoniazid and 0.6% were multi-drug resistant. No increasing trend was observed, but in view of the international emergence of resistance, the PHLS, together with colleagues in Scotland and Northern Ireland, established a surveillance system 'MYCOBNET', collecting prospective data for the whole of the UK. Isoniazid resistance rates (with or without resistance to other drugs) were 4.6%, 5.4% and 5.5% in 1993, 1994 and 1995 respectively. Multi-drug resistance rose from 0.6% in 1993 to 1.2% in 1994 and 1995.

10.8.2 RESISTANCE IN OTHER COUNTRIES

Resistance rates in *Mycobacterium tuberculosis* are higher in the USA, where a 1993–96 survey estimated that 8.4% of isolates were initially resistant to isoniazid and 2.2% were multi-drug resistant [89]. Compared with previous US surveys in 1991 and 1992, isoniazid resistance had remained relatively stable and multi-drug resistance had decreased a little. In some parts of the developing world multi-drug resistance is especially frequent.

10.9

FUNGAL INFECTIONS

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

10.9.1 RESISTANCE TO ANTIFUNGAL AGENTS

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

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

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

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

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

TABLE 16

ANTIFUNGAL AGENTS AVAILABLE IN THE UK

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

10.10

VIRAL INFECTIONS

10.10.1 EVOLUTION OF ANTIVIRAL RESISTANCE

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

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

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

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

- a) **Mutation rate** Resistance is caused by single or multiple mutations. As with bacteria, mutants exist within the individual's viral population prior to therapy but a drug's selective pressure encourages their expansion to become the majority population. RNA viruses (eg HIV), do not 'proof-read' genes during replication and so generate resistant mutants more rapidly than DNA viruses (eg the herpes family) which do proof-read. In addition, the risk of resistant mutants emerging depends on the total number of virus particles and on their replication rate. Chronic infections with rapid turnover, eg HIV, HCV and HBV are ideally suited to the development of resistance. Reduced immune function increases the viral load and replication rate, also increasing the risk of resistance.
- b) **Viral 'fitness'** Viruses are exquisitely adapted to their hosts. Drug-selected mutants may initially have reduced fitness but, as with bacteria (see Section 13.2) there are now many examples of 'compensatory' mutations that allow these resistant mutants to regain their fitness.
- c) **Drug potency** If a drug completely stops viral replication, resistance should not appear. In contrast, a drug with minimal potency will not exert sufficient selective pressure to generate resistance. The ideal circumstances in which resistance will occur arise where potent antiviral agents are used suboptimally, eg as monotherapy or dual therapy for HIV, or where there is poor drug compliance.

TABLE 17

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

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

10.10.2 RESISTANCE IN CLINICALLY IMPORTANT VIRUSES

10.10.2.1 Herpes viruses

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

10.10.2.2 Herpes simplex virus (HSV)

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

10.10.2.3 Varicella-Zoster (VZV) and cytomegalovirus

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

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

10.10.2.4 Hepatitis B (HBV)

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

10.10.2.5 Human immunodeficiency virus (HIV)

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

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

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

10.10.2.6 Influenza

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

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

10.10.3 TRANSMISSION OF RESISTANT VIRUSES

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

10.10.3.1 Herpes viruses

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

10.10.3.2 HIV

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

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

10.10.3.3 Influenza

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

10.11

WHAT NEXT FOR ANTIMICROBIAL RESISTANCE?

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

Several key developments can be predicted.

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

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

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

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

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

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

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

KEY POINTS

Resistance is greatest where use of antimicrobial agents is heaviest

Major problem areas in hospitals include ICUs and transplant units

Key patient groups include the immunocompromised

Resistance is also increasing in common community pathogens

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

11.1

INTENSIVE CARE UNITS

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

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

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

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

‘Intensive care not intensive antibiotics!’

TABLE 18**RESISTANCE (%) OF PSEUDOMONAS AERUGINOSA ISOLATES BY PATIENT GROUP: UK**

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

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

11.2**ADMISSIONS WARDS**

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

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

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

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

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

11.3

OTHER IN-PATIENTS

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

11.4

IMMUNOCOMPROMISED PATIENTS, INCLUDING THOSE WITH HIV INFECTION

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

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

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

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

11.5

OUT-PATIENTS

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

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

BOX 9

ENDOCARDITIS (INFECTION OF THE HEART VALVES)

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

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

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

11.6

DENTAL USE OF ANTIMICROBIAL AGENTS

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

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

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

TABLE 19**ANTIBACTERIAL AGENTS PRESCRIBED BY DENTISTS AS PERCENTAGES OF ALL AGENTS DISPENSED IN THE COMMUNITY IN ENGLAND, 1993–96**

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

Data source: Statistics Division of the Department of Health.