The need for new antibiotics

D.M. Livermore

Antibiotic Resistance Monitoring & Reference Laboratory, Specialist & Reference Microbiology Division, Health Protection Agency, London, UK

ABSTRACT

Politicians and public health officials have joined specialist professionals in recognising antibiotic resistance as a threat to modern medicine. Their response has centred on minimising unnecessary antibiotic prescribing, aiming to reduce selection pressure for resistance. Despite a few hopeful trends (e.g., declining penicillin resistance among pneumococci in the UK), established resistance is proving hard to displace; moreover, new resistances continue to emerge and to proliferate at new sites. There consequently remains a strong need for new antibiotics, particularly those directed against multiresistant Gram-negative bacteria in hospitals. Already some nonfermenters of the genera *Acinetobacter* and *Pseudomonas* are resistant to all good antibiotics and many Enterobacteriaceae are resistant to all except carbapenems. There is also a growing need for new agents against community-acquired pathogens, including the agents of tuberculosis, gonorrhoea and urinary tract infections. Unless antibacterial development is re-energised, there is a serious risk that a growing proportion of infections, especially in hospitals, will become effectively untreatable.

Keywords Antibiotics, multiresistance, pharmaceutical development

INTRODUCTION

Antibiotics have revolutionised medicine, allowing treatment of infections that were once widely fatal and safeguarding procedures that were once unthinkable. Their availability has created an assurance of health unknown to previous generations. This assurance, now taken for granted, will be dissipated if resistance development continues to outstrip antibiotic development, as in the past decade.

Selection of resistance is an inevitable, Darwinian consequence of antibiotic usage, though its frequency varies with: (i) the regimens and extent of use, (ii) the effectiveness of infection control, and (iii) random factors, such as the initial escape of resistance genes to mobile DNA and into biologically 'fit' strains. No antibiotic escapes all resistance and, if one did so, its likely effect would be to shift the microbial ecology in favour of more resilient opportunist pathogens, able to exploit the vacated niche.

Concern about resistance has escalated in the past 5–6 years, with reports by, amongst others, the British House of Lords [1], UK Department of Health [2], European Commission [3], World Health Organization [4] and an inter-agency force in the USA [5]. These reports all argue for reduced antibiotic use, for better-tailored use (i.e., appropriate drug, dose and duration), and for better infection control. Perhaps because of these reports, along with subsequent press coverage and governmental advertising, community use of antibiotics in the UK has fallen *c.* 23% since 1997 [6], with a greater reduction in prescribing to children. Meanwhile, antimicrobial prescriptions to ambulatory patients in the USA have declined over 20% [7] and the use of antibiotics as growth promoters in animal husbandry has been banned in the EU. Some improvements in resistance trends have followed these reductions, though causality is hard to prove. Penicillin nonsusceptibility among pneumococci is declining in prevalence in the UK (Fig. 1) and, following the ban

Corresponding author and reprint requests: D.M. Livermore, Antibiotic Resistance Monitoring & Reference Laboratory, Specialist & Reference Microbiology Division, Health Protection Agency, London NW9 5HT, UK
E-mail: david.livermore@hpa.org.uk
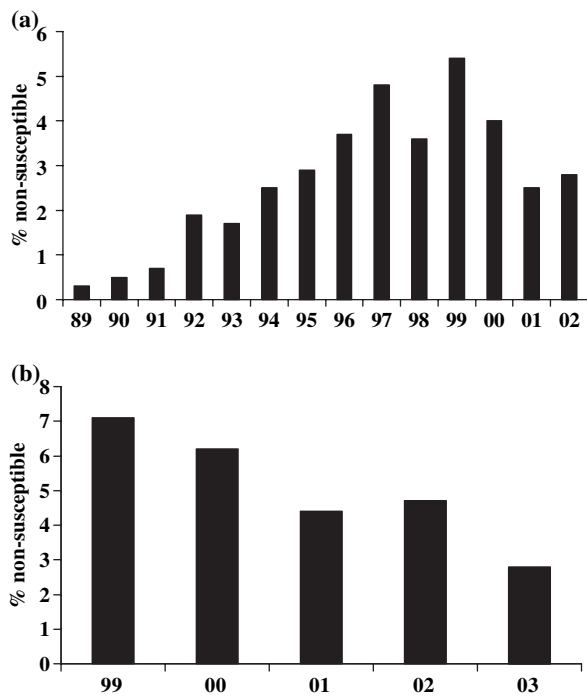
Fig. 1. Prevalence of penicillin nonsusceptibility in invasive *S. pneumoniae* based (a) on reports to the Health Protection Agency for most laboratories in England and Wales and (b) on sentinel surveillance of 23 UK hospitals under the European Antimicrobial Resistance Surveillance System (http//:http://www.earss.rivm.nl). Both studies confirm falling resistance.

on growth promotors, there has been a decline in several resistances, including to vancomycin, among enterococci from poultry and pigs in Denmark [8]. Vancomycin resistance in clinical enterococci in England and Wales is falling too, from a peak of nearly 30% in 1999 to 17% in 2002. These, though, are isolated successes and, as a whole, resistance has continued to accumulate in the past 5–6 years with critical new types continuing to emerge, as with vancomycin-resistant *Staphylococcus aureus*, or to increase in prevalence and geographic range, as with carbapenemases in nonfermenters, ciprofloxacin-resistant gonococci and CTX-M β-lactamases.

Before reviewing particular concerns, it should be said that there are sound reasons to doubt whether reductions in antibiotic use can be achieved or maintained at a sufficient degree to substantially reverse growing resistance. Cessation of use, as with growth promoters, is not an option for therapeutic drugs, and the objectives of reducing usage and selection pressure are counter-poised by social and economic factors,

including (i) ageing populations, with a growing body of vulnerable patients who migrate between hospitals and nursing homes, re-circulating resistant strains [9,10]; (ii) advances elsewhere in medicine, which enlarge the pool of immunosuppressed and vulnerable patients; (iii) globalisation of peoples and produce, spreading resistance among countries, as with the introduction of penicillin-resistant pneumococci to Iceland by returning holiday-makers and their subsequent spread in socialised childcare [11]; and (iv) by stressed healthcare systems, where patient throughput receives highest priority. What is more, a growing body of data shows that many resistant bacteria are biologically fit or, if not immediately so, undergo compensatory mutations that offset the fitness cost of resistance, meaning that they are difficult to displace. Against this background it is naïve to anticipate that small improvements or reductions in antibiotic use can hugely turn the tide of resistance [12,13].

It follows that antibiotic development remains vital if man is to keep ahead of resistance, and it is partly reassuring that, despite press hype, some new agents do continue to be developed (Table 1). The word 'partly' is used because it is not clear where the *next* antibiotics will come from, and because of a mismatch between what is needed and what is developed.

Table 1. Spectra of antibiotics recently launched, or anticipated by 2008

Gram-positive cocci only	Respiratory pathogens	Broad spectrum
Quinupristin/ dalfopristin (not *E. faecalis*)	Telithromycin	Ertapenem[c]
Linezolid	Peptide deformylase inhibitors	Doripenem[c]
Daptomycin	Moxifloxacin[b]	Tigecycline
Oritavancin	Garenoxacin[b]	Sitafloxacin
Dalbavancin (not Van A VRE)	Gemifloxacin[b]	
Anti-MRSA cephalosporins[a]		

[a]Have broad-spectrum activity but tailored vs. MRSA.
[b]Have broad-spectrum activity but tailored vs. *S. pneumoniae* and no better than ciprofloxacin vs. Gram-negative bacteria.
[c]Not active against strains resistant to existing carbapenems.

NEED FOR NEW ANTIBIOTIC VERSUS NOSOCOMIAL INFECTIONS

The need for new agents is most pressing in hospital infections, where small but growing numbers of isolates, mostly Gram-negative non-fermenters of the genera *Acinetobacter and Pseudomonas*, are resistant to all 'good' antibiotics and where growing numbers of Enterobacteriaceae are resistant to all except carbapenems. Whilst there is a lesser shortage of agents active against staphylococci, the prevalence of infections with methicillin-resistant *Staphylococcus aureus* (MRSA) remains extremely high in many countries.

Acinetobacter and *Pseudomonas* spp.

These genera account for 10% of in-patient infections (Table 2), but for a higher proportion in, for example, intensive care and burns units. *P. aeruginosa* is also important as a pulmonary pathogen in cystic fibrosis. Along with rarer nonfermenters these species account for most of the cases where we, as a national reference laboratory, encounter strains resistant to all 'good' antibiotics. *Acinetobacter* spp. (principally *Acineto-*

Table 2. Relative prevalence of major pathogens among in-patient infections and in bacteraemias

Organism	All in-patient isolates,UK & Ireland, 2001 (%)	Bacteraemias 2001,England & Wales (%)
E. coli	18.3	21.1
Klebsiella spp.	4.4	5.7
P. mirabilis	3.1	3.3
AmpC-inducible Enterobacteriaceae[a]	6.9	3.3
P. aeruginosa	10.0	3.2
Acinetobacter spp.	1.1	0.8
Methicillin-susceptible *S. aureus*	18.4	13.1
MRSA	14.8	9.9
Coagulase-ve staphylococci	6.6	10.7
S. pneumoniae	2.2	6.7
α- and nonhaemolytic streptococci	0.9	3.5
β-Haemolytic streptococci	4.8	3.0
Enterococci	4.8	7.1
Others	3.6	8.6

[a]Includes *Enterobacter* spp., *Citrobacter* spp., *Morganella morganii* and *Serratia* spp.
Data: Health Protection Agency and Livermore et al. [14]

bacter baumannii) are notorious for their capacity to accumulate resistance, and for their tenacity. They frequently cause clonal outbreaks, which can be extremely difficult to terminate, even with cohorting of patients, sterilisation of equipment, reinforcement of handwashing, and deep-cleaning of facilities. Throughout the 1980s and 1990s *A. baumannii* became progressively more-often resistant to cephalosporins and fluoroquinolones, having previously become widely resistant to penicillins and aminoglycosides [15]. By the mid-1990s, carbapenems were the treatment mainstay and no longer the reserve.

Now, carbapenem resistance is increasing steadily, variously mediated by acquired VIM and IMP metallo-β-lactamases, OXA carbapenemases and combinations of weak, poorly characterised carbapenemases, together with reduced drug accumulation [16]. This increase is illustrated for the USA in Fig. 2, but the position is worse in South America and in the Far East [17] whilst, in South-east England, three carbapenem-resistant strains, each with subvariants, are circulating in up to 50 hospitals each, with these numbers growing steadily [18]. The most prevalent of these latter strains has an unknown mechanism of carbapenem resistance; the others have OXA-23 enzyme.
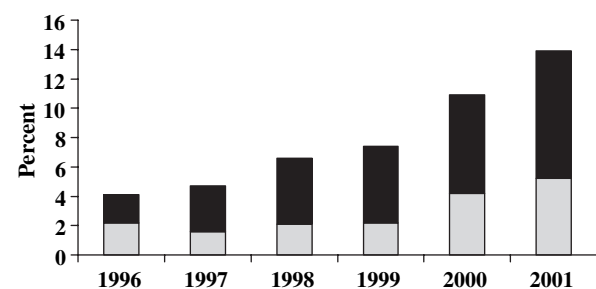
Some carbapenem-resistant acinetobacters remain susceptible to sulbactam, or to one or more aminoglycosides, but these sensitivities are not universal and aminoglycoside-modifying enzymes are frequent, notoriously including APH(3')-VI, which affects amikacin and isepamicin – otherwise the most enzyme-resistant analogues [19]. Most isolates, including those
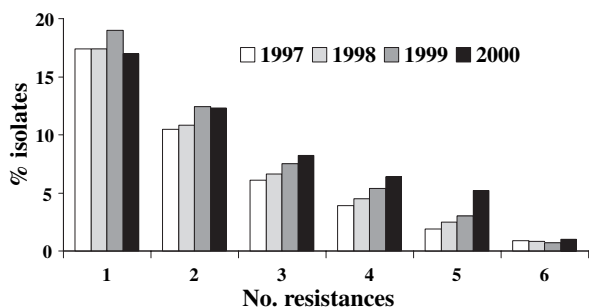
Fig. 2. Rising carbapenem resistance (black) or intermediate resistance (grey) among *Acinetobacter* spp. isolates at 250 US hospitals, as reported to the TSN-Databases®. Resistances to other agents are already hugely frequent in the genus. Reproduced with permission from Livermore [21].

resistant to carbapenems, remain susceptible to polymyxins B and E (colistin), but these are, rather, nephrotoxic compounds with poor efficacy in the case of pneumonias – a common infection site [20,21]. Minocycline, too, is widely active, but would not ordinarily be considered appropriate in the case of severe infections.

P. aeruginosa is a more frequent pathogen than *A. baumannii*, accounting for 10% of in-patient isolates and 3.2% of all bacteraemias in the UK [Table 2]. Resistance is less frequent than in *Acinetobacter* spp. and, based on US data, rates to β-lactams and aminoglycosides remain around 5–15% with only fluoroquinolone resistance rising steadily [22]. These figures, however, disguise much higher resistance rates in many burns, intensive care, and cystic fibrosis units and deeper analysis (Fig. 3) shows rising proportions of isolates multi-resistant to two to five of six index antibiotics [23].

Multi-resistance in *P. aeruginosa* can reflect the accumulation of successive mutations that derepress chromosomal β-lactamase, up-regulate multi-drug efflux, reduce permeability and diminish topoisomerase sensitivity to quinolones [23]. This accumulation may be accelerated by co-selection of hypermutability with a first resistance, especially in cystic fibrosis patients [24]. Alternatively, multiresistance can reflect the acquisition of plasmids or integrons encoding combinations of β-lactamase and aminoglycoside-modifying enzymes [23]. Several integrons (natural genetic recombination systems) can encode IMP, VIM or SPM metallo-β-lactamases together with AAC[6']

aminoglycoside acetyltransferases, conferring resistance to all aminoglycosides and β-lactams, except sometimes, aztreonam. Such strains – many of them independently resistant to fluoroquinolones – have been reported in Japan since the late 1980s and, since 1997, from a growing list of countries in Asia, Europe and the Americas [21]. Major outbreaks of producers have occurred in Greece, Korea, Hong Kong, Brazil and Colombia [25,26], some lasting months or years, others with the strain(s) spreading among multiple hospitals. Most multiresistant *P. aeruginosa* remain susceptible to polymyxins, but, as with *Acinetobacter* infections, efficacy is uncertain, especially in pneumonias [20].

Among the compounds listed in Table 1, sitafloxacin is slightly more active than ciprofloxacin against fluoroquinolone-susceptible *A. baumannii* strains, but none of the fluoroquinolones is superior to ciprofloxacin against *P. aeruginosa* and none is reliably active against *Acinetobacter* strains with high-level ciprofloxacin resistance. Tigecycline, the novel tetracycline [Table 1], is active against *A. baumannii* but, as with minocycline, there is a need to establish clinical efficacy in severe infection; it is not active against *P. aeruginosa*.

In short, nonfermenters account for about 10% of in-patient infections, though for a smaller proportion of bacteraemias. They are becoming more resistant, and more-often resistant to all good drugs. Few of the new agents listed in Table 1 show promise against *Acinetobacter* spp.; none does so against *P. aeruginosa*. It is here that we are closest to the much-feared 'end of antibiotics'.

Enterobacteriaceae

Pan-resistance remains extremely rare in nosocomial Enterobacteriaceae, because carbapenems retain near-universal activity [21]. Resistance to other agents is rising steadily, however, and two trends must be particularly highlighted.

First, the utility of the fluoroquinolones is eroding. This is illustrated, for England and Wales, in Fig. 4, which shows rising ciprofloxacin resistance trends in *Klebsiella and Enterobacter* bacteraemias (mostly hospital-acquired) as well as *E. coli* bacteraemias (variously hospital- and community-acquired) [27]. Karlowsky et al. [28] have reported similar results in the USA, with

Fig. 3. Proportion of *P. aeruginosa* isolates resistant to 1–6 agents among ceftazidime, piperacillin, imipenem, amikacin, gentamicin and ciprofloxacin among those reported from >250 laboratories to the TSN-Databases®. Note the growing proportions resistant to two to five of these core antipseudomonal agents. Reproduced with permission from Livermore [23].
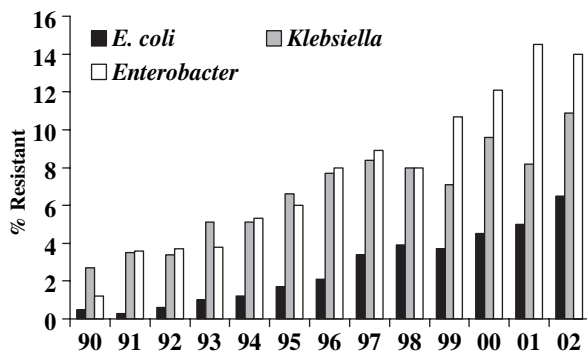
Fig. 4. Growing proportions of *E. coli* (black) *Klebsiella* spp. (grey) and *Enterobacter* spp. (white) resistant to ciprofloxacin. Based on reports to the Health Protection Agency for bacteraemias from most clinical laboratories in England and Wales (updated from Ref. 27).

Fig. 5. Proportions of *Klebsiella* spp., *E. coli* and *Proteus mirabilis* with ESBLs, based on data reported under the SENTRY surveillance [34]. Note that high rate of ESBLs in Latin America, perhaps reflecting the early dissemination of CTX-M enzymes in this region. These enzymes are now spreading worldwide.

ciprofloxacin and levofloxacin resistance rates rising from 6 to 11% between 1998 and 2001. Whilst these rises are significant, the prevalence rates remain low compared to Far East, India and South America.

Second, the proportion of Enterobacteriaceae resistant to third-generation cephalosporins continues to grow. Such resistance often arises through mutational hyper-production of chromosomal AmpC β-lactamases in *Enterobacter* spp., *Citrobacter freundii*, *Morganella morganii*, *Serratia* and *Providencia* spp. This mechanism and its contingent resistance is seen in 30–40% of *Enterobacter* spp. isolates worldwide, with local rates up to 70%. Even if a strain is susceptible at first isolation there is a substantial risk (c. 20% in a bacteraemia) that derepressed mutants will be selected in cephalosporin therapy, meaning that these drugs cannot be perceived as reliable in infections caused by these species [29,30]. Cephalosporin resistance also can arise via acquisition of plasmids encoding 'extended-spectrum β-lactamases' (ESBLs). Until recently, most ESBLs outside South America were mutants of the classical TEM and SHV β-lactamases that have long been a source of resistance to penicillins in Enterobacteriaceae. Such mutant enzymes are most prevalent in nosocomial *Klebsiella* spp., occurring in c. 25% of intensive care isolates of this genus in Europe [31] and a few ESBL-producing strains of *K. pneumoniae* and *Enterobacter aerogenes* have achieved epidemic spread among hospitals [32,33]. Many ESBL producers, including these
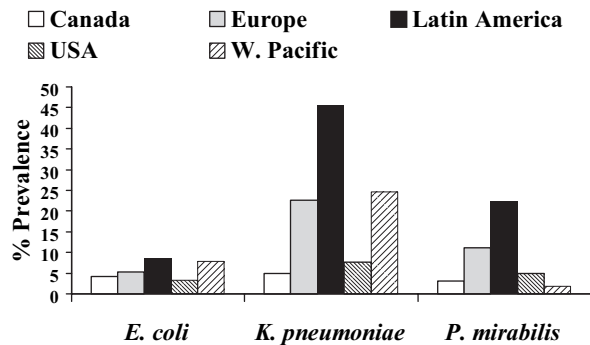
epidemic strains, are multiresistant also to fluoroquinolones and aminoglycosides.

ESBLs are more prevalent in South America than elsewhere [34] (Fig. 5) and the types are different, too at least in the southern 'cone' of the continent, where 'CTX-M' enzymes predominate [35,36]. CTX-M enzymes are not TEM or SHV mutants but, rather, have evolved by the escape and genetic modification of the chromosomal β-lactamases of *Kluyvera* spp. In the past 5 years, CTX-M enzymes have also begun to spread widely in Europe (especially Eastern Europe), Asia and North America. In parts of Europe, China and Russia they are overtaking TEM and SHV-related ESBLs in prevalence and, in the UK, are spreading dramatically into community *Escherichia coli* (see below).

The result of rising quinolone and cephalosporin resistance is to drive carbapenem use. Thus far, even 19 years after imipenem's launch, these agents retain near-universal activity against nosocomial Enterobacteriaceae [21] with resistance only arising when a potent carbapenemase is present in a remarkably impermeable strain. It is uncertain if this assurance will last once carbapenems are used more heavily – as they will be with the erosion of cephalosporin and quinolone activity. If the carbapenem activity were lost, many infections would become effectively untreatable. Among the noncarbapenems listed in Table 1, only the fluoroquinolones and tigecycline are active against Enterobacteriaceae, and the best new quinolone (sitafloxacin) has only marginal activity against

isolates resistant to ciprofloxacin. Tigecycline is almost universally active against Enterobacteriaceae except Proteeae (which are resistant to all tetracyclines), but it will require a major shift in practice to accept a tetracycline for use in the case of severe nosocomial infections.

Nosocomial Gram-positive bacteria

Methicillin-resistant *Staphylococcus aureus* (MRSA) are the single most important hospital pathogens in many countries. In the UK, they account for 15% of all clinically significant in-patient isolates and 10% of bacteraemias (Table 2) and, whilst their prevalence remains low in Scandinavia and the Netherlands (1–2%), it is high or rising elsewhere (Fig. 6) placing a major burden on healthcare systems [37]. MRSA evolve rarely and their epidemiology reflects the spread of a few strains among many patients; in the UK, just two strains account for 95% of MRSA bacteraemias [38].

There is now little shortage of drugs active against MRSA. Vancomycin, teicoplanin, quinupristin/dalfopristin, linezolid and daptomycin have nearly universal *in vitro* activity, as do the developmental agents tigecycline, oritavancin and dalbavancin. In addition, many MRSA remain susceptible to fusidic acid, minocycline, trimethoprim and rifampicin, which may be used in combination. A growing proportion of MRSA isolates, in several European countries, are regaining susceptibility to gentamicin. The problem with MRSA is not resistance *per se*, but tenacity and the fact that vancomycin, still the standard
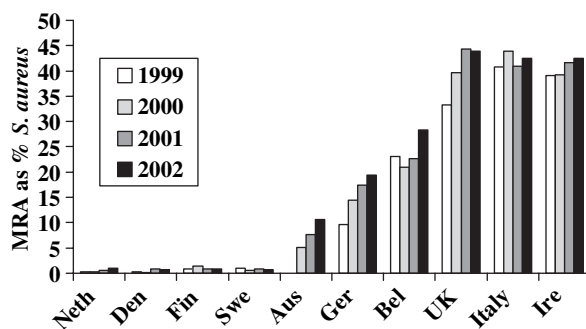

Fig. 6. MRSA as a percentage of *S. aureus* bacteraemias in countries with extensive reporting (>250 *S. aureus* bacteraemias in ≥3 of 4 years) to the European Antimicrobial Resistance Surveillance System (http://www.earss.rivm.nl). Despite high profile and the availability of anti-MRSA agents there is no evidence of reducing prevalence.

therapy, is poorly effective. Newer agents (notably linezolid) may be superior in some settings [39] but this remains to be established more widely. Thus far, too, there is little evidence to suggest that they can 'beat' the MRSA problem in the way that methicillin 'beat' penicillin-resistant staphylococcus in the 1960s. β-Lactams are superior to vancomycin against methicillin-susceptible *S. aureus*, giving the implication that, if analogues active against MRSA could be developed, these might have great potential. Two such agents, RWJ-54428 (Johnson & Johnson, Raritan, NJ, USA) [40] and BAL 9141 (Basilea, Basel, Switzerland) [41], are presently in clinical development, but the area is difficult, with many previous anti-MRSA β-lactams having been abandoned.

The need for new anti-enterococcal agents is less acute, not only because many of the compounds listed in Table 1 are active but also because fewer patients are infected than with MRSA. Nevertheless enterococcal endocarditis remains a problem when it is caused by a vancomycin-resistant strain that also has high-level resistance to aminoglycosides and either (i) the organism is *Enterococcus faecium*, which is inherently resistant to ampicillin or (ii) the patient is allergic to ampicillin. Treatment is considered to require bactericidal activity and, among the agents in Table 1, only daptomycin and oritavancin meet this criterion, with their clinical efficacy in the setting still to be established.

NEED FOR NEW ANTIBIOTICS IN THE COMMUNITY

There is a much clearer association between species and infection type in community-acquired infection than in hospitals, where opportunists can attack many sites in vulnerable patients. Consequently, it is better to organise this section by indication than by organism.

Respiratory infections account for over half of all community antibiotic prescribing, much of it inappropriate. The size of this market explains why many of the developmental antibiotics listed in Table 1 are tailored against respiratory infections but, whatever the commercial logic, the medical need for new agents is much less here than in the context of nosocomial infection. Amongst the major pathogens, *H. influenzae* and *M. catarrhalis* remain almost universally susceptible to oral third-generation cephalosporins and

fluoroquinolones, and although there is concern about resistance in *S. pneumoniae*, this seems to be much scarcer when clinical trails seek to recruit consecutive patients than in laboratory surveys. In any event, increasing deployment of vaccination targeted against the serotpyes where resistance is most frequent, looks set to impact on the incidence of severe pneumococcal infection.

The community-acquired respiratory infection for which there *is* a need for new agents is tuberculosis, where resistance continues to increase in many developing countries [42], especially those where the public health infrastructure has crumbled. With increasing human migration, these resistant strains are likely to be increasingly imported into developed countries.

In the case of urinary infections (the second commonest reason for community prescribing of antibiotics) there is frequent resistance to ampicillin and trimethoprim in *E. coli* and, in many parts of the world, rising resistance to fluoroquinolones. More disturbingly CTX-M β-lactamases are achieving greater penetration into community isolates than did earlier ESBLs. Many UK counties are presently seeing urinary infections with CTX-M-15-producing *E. coli* resistant to penicillins, cephalosporins, quinolones and trimethoprim, mostly among patients with some recent hospital contact. The oral treatment options narrow to nitrofurantoin, which cannot be used empirically as it is not active against Proteeae, and fosfomycin, where mutational resistance can readily emerge. The alternative is to admit the patient and administer a carbapenem, adding cost and complexity [43].

Gonorrhoea is perhaps a surprising inclusion on a list of infections where new drugs are needed. Nevertheless, it is an infection where sudden shifts in resistance occur, owing to rapid dissemination of resistant strains by treatment failures. The 1970s saw a dramatic spread of β-lactamase-producing strains in the Far East, and, similarly, the present decade is seeing escalating resistance to fluoroquinolones [44]. For example, the UK had only rare, largely imported, cases of ciprofloxacin-resistant gonorrhoea until 2001; by 2002, however, there was domestic transmission of resistant clones and a rise in the prevalence of resistance to over 10%, compared with 2–3% in 2000–1 [44,45]. Only the third-generation cephalosporins or spectino-

mycin now meet the objective of achieving a 95% cure rate.

CONCLUSION

Even with more appropriate prescribing, it seems likely that antibacterial resistance will continue to accumulate in many pathogens and settings, especially in hospitals. Clinicians already see pan-resistance to 'good' antibiotics in isolates of *P. aeruginosa* and *Acinetobacter* spp., and the absence of pan-resistance in Enterobacteriaceae is only due to the continued efficacy of the carbapenems. If carbapenemases do spread widely we will face a situation where many nosocomial Gram-negative infections become effectively untreatable. It is here, against Gram-negative opportunists, that the medical need for new agents is most acute and where, apart from tigecycline, there are few new agents in advanced development. And, whilst new treatments are becoming available for infections caused by multiresistant Gram-positive pathogens, the goal of finding a drug that is as effective, against MRSA, as penicillin was against staphylococci in the 1940s remains elusive. In the community, multiresistance is complicating the treatment of urinary tract infections, gonorrhoea and tuberculosis, though problems with *S. pneumoniae* may have been over-stated.

The medical need for new antibiotics is clear. What is less clear is the commercial logic. The proportion of infections that cannot be treated with present agents is small, restricting demand, and the infections are widely scattered, complicating clinical trials. As other articles in this supplement will show, many of the largest pharmaceutical companies have concluded that drugs directed against chronic diseases offer a better revenue stream than antibacterial agents, where the courses are short and restriction is likely. Several major houses have abandoned antibacterial development and others have merged, leaving one developer where there previously were two or more. Some small pharma and biotech companies do seek to develop antibiotics but most depend on venture capital not sales income and, with the present regulatory burden, face huge barriers to market entry. These barriers were raised with the best intentions of ensuring public safety but will have the opposite effect if they stave off antibiotic development whilst resistance continues to accumulate.

REFERENCES

1. House of Lords Select Committee on Science and Technology. *Resistance to Antibiotics and Other Antimicrobial Agents*, Session 1997–8. TSO 1998.
2. UK Standing Medical Advisory Committee (SMAC). *The Path of Least Resistance*. Department of Health, London 1998.
3. European Commission BD. Opinion of the Scientific Steering Committee on Antimicrobial Resistance, Brussels 2003.
4. Anonymous. *WHO global strategy for containment of antimicrobial resistance.* Geneva: World Health Organization 2001.
5. Interagency Task Force on Antibiotic Resistance. A public health plan to combat antimicrobial resistance. http://www.cdc.gov/drugresistance/actionplan/actionplan.pdf. 2003.
6. Livermore DM. Bacterial resistance. origins, epidemiology, and impact. *Clin Infect Dis* 2003; **36** (Suppl. 1)**:** S11–S23.
7. Gruneberg RN. Global surveillance through PROTEKT. the first year. *J Chemother* 2002; **14** (Suppl. 3)**:** 9–16.
8. Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, Bager F. Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob Agents Chemother* 2001; **45:** 2054–9.
9. Mendelson G, Yearmack Y, Granot E, Ben Israel J, Colodner R, Raz R. *Staphylococcus aureus* carrier state among elderly residents of a long-term care facility. *J Am Med Dir Assoc* 2003; **4:** 125–7.
10. Wiener J, Quinn JP, Bradford PA et al. Multiple antibiotic-resistant *Klebsiella* and *Escherichia coli* in nursing homes. *JAMA* 1999; **281:** 517–23.
11. Soares S, Kristinsson KG, Musser JM, Tomasz A. Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. *J Infect Dis* 1993; **168:** 158–63.
12. Gillespie SH. Antibiotic resistance in the absence of selective pressure. *Int J Antimicrob Agents* 2001; **17:** 171–6.
13. Lenski RE. The cost of antibiotic resistance – from the perspective of a bacterium. *Ciba Found Symp* 1997; **207:** 131–40.
14. Livermore DM, Mushtaq S, James D et al. In-vitro activity of piperacillin/tazobactam and other broad-spectrum antibiotics against bacteria from hospitalised patients in the British Isles. *Int J Antimicrob Agents* 2003; **22:** 14–27.
15. Bergogne-Berezin E, Towner KJ. *Acinetobacter* spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. *Clin Microbiol Rev* 1996; **9:** 148–65.
16. Nordmann P, Poirel L. Emerging carbapenemases in Gram-negative aerobes. *Clin Microbiol Infect* 2002; **8:** 321–31.
17. Jones RN, Sader HS, Beach ML. Contemporary in vitro spectrum of activity summary for antimicrobial agents tested against 18569 strains non-fermentative Gram-negative bacilli isolated in the SENTRY Antimicrobial Surveillance Program (1997–2001). *Int J Antimicrob Agents* 2003; **22:** 551–6.
18. Coelho JM, Woodford N, Turton J, Livermore DM. Multiresistant *Acinetobacter* in the UK. how big a threat? *J Hosp Infect* 2004; in press.
19. Lambert T, Gerbaud G, Courvalin P. Transferable amikacin resistance in *Acinetobacter* spp. due to a new type of 3′-aminoglycoside phosphotransferase. *Antimicrob Agents Chemother* 1988; **32:** 15–9.
20. Levin AS, Barone AA, Penco J et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Clin Infect Dis* 1999; **28:** 1008–11.
21. Livermore DM. Threat from the pink corner. *Ann Med* 2003; **35:** 226–34.
22. Karlowsky JA, Draghi DC, Jones ME, Thornsberry C, Friedland IR, Sahm DF. Surveillance for antimicrobial susceptibility among clinical isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from hospitalized patients in the United States, 1998–2001. *Antimicrob Agents Chemother* 2003; **47:** 1681–8.
23. Livermore DM. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*, our worst nightmare? *Clin Infect Dis* 2002; **34:** 634–40.
24. Oliver A, Canton R, Campo P, Baquero F, Blazquez J. High frequency of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis lung infection. *Science* 2000; **288:** 1251–4.
25. Lee K, Lim JB, Yum JH et al. bla(VIM-2) cassette-containing novel integrons in metallo-β-lactamase-producing *Pseudomonas aeruginosa* and *Pseudomonas putida* isolates disseminated in a Korean hospital. *Antimicrob Agents Chemother* 2002; **46:** 1053–8.
26. Gales AC, Menezes LC, Silbert S, Sader HS. Dissemination in distinct Brazilian regions of an epidemic carbapenem-resistant *Pseudomonas aeruginosa* producing SPM metallo-β-lactamase. *J Antimicrob Chemother* 2003; **52:** 699–702.
27. Livermore DM, James D, Reacher MH et al. Trends in fluoroquinolone (ciprofloxacin) resistance among Enterobacteriaceae from bactermias in England and Wales 1990–1999. *Emerg Infect Dis* 2002; **8:** 473–8.
28. Karlowsky JA, Jones ME, Thornsberry C, Friedland IR, Sahm DF. Trends in antimicrobial susceptibilities among Enterobacteriaceae isolated from hospitalized patients in the United States from 1998 to 2001 *Antimicrob Agents Chemother* 2003; **47:** 1672–80.
29. Chow JW, Fine MJ, Shlaes DM et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991; **115:** 585–90.
30. Livermore DM, Brown DF, Quinn JP, Carmeli Y, Paterson DL, Yu VL. Should third-generation cephalosporins be avoided against AmpC-inducible Enterobacteriaceae? *Clin Microbiol Infect* 2004; **10:** 84–5.
31. Yuan M, Aucken H, Hall LM, Pitt TL, Livermore DM. Epidemiological typing of klebsiellae with extended-spectrum β-lactamases from European intensive care units. *J Antimicrob Chemother* 1998; **41:** 527–39.
32. Arlet G, Rouveau M, Casin I, Bouvet PJ, Lagrange PH, Philippon A. Molecular epidemiology of *Klebsiella pneumoniae* strains that produce SHV-4 β-lactamase and which were isolated in 14 French hospitals. *J Clin Microbiol* 1994; **32:** 2553–8.
33. De Gheldre Y, Struelens MJ, Glupczynski Y et al. National epidemiologic surveys of *Enterobacter aerogenes* in Belgian Hospitals from 1996 to 1998. *J Clin Microbiol* 2001; **39:** 889–96.
34. Winokur PL, Canton R, Casellas JM, Legakis N. Variations in the prevalence of strains expressing an extended-spectrum β-lactamase phenotype and characterization of

isolates from Europe, the Americas, and the Western Pacific region. *Clin Infect Dis* 2001; **32** (Suppl. 2)**:** S94–103.

35. Radice M, Power P, Di Conza J, Gutkind G. Early dissemination of CTX-M-derived enzymes in South America. *Antimicrob Agents Chemother* 2002; **46:** 602–4.

36. Bonnet R. Growing group of extended-spectrum β-lactamases: the CTX-M enzymes. *Antimicrob Agents Chemother* 2004; **48:** 1–14.

37. Cooper BS, Stone SP, Kibbler CC *et al.* Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling. *Health Technol Assess* 2003; **7:** 1–194.

38. Johnson AP, Aucken H, Cavendish S *et al.* Dominance of EMRSA-15 and -16 among MRSA causing nosocomial bacteraemia in the UK. Analysis of isolates from the European Antimicrobial Resistance Surveillance System (EARSS). *J Antimicrob Chemother* 2001; **48:** 144.

39. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest* 2003; **124:** 1789–97.

40. Johnson AP, Warner M, Carter M, Livermore DM. In vitro activity of cephalosporin RWJ-54428 (MC-02479) against multidrug-resistant gram-positive cocci. *Antimicrob Agents Chemother* 2002; **46:** 321–6.

41. Entenza JM, Hohl P, Heinze-Krauss I, Glauser MP, Moreillon P. BAL9141, a novel extended-spectrum cephalosporin active against methicillin-resistant *Staphylococcus aureus* in treatment of experimental endocarditis. *Antimicrob Agents Chemother* 2002; **46:** 171–7.

42. Zumia A, Grange JM. Multidrug-resistant tuberculosis – can the tide be turned? *Lancet Infect Dis* 2001; **1:** 199–202.

43. Woodford N, Ward E, Kaufmann CE. Community and hospital spread of *Escherichia coli* producing CTX-M extended-spectrum β-lactamases (ESBLs) in the UK. *J Antimicrob Chemother*; in press.

44. Fenton KA, Ison C, Johnson AP *et al.* Ciprofloxacin resistance in *Neisseria* gonorrhoeae in England and Wales in 2002. *Lancet* 2003; **361:** 1867–9.

45. Corkill JE, Komolafe AJ, Neal TJ, Mortimore A, Alawattegama AB, Hart CA. Molecular epidemiology of endemic ciprofloxacin-resistant *Neisseria gonorrhoeae* in Liverpool. *Int J STD AIDS* 2003; **14:** 379–85.