Nevertheless, bacteraemia surveillance for England and Wales showed that resistance was slowly accumulating in *Klebsiella* and *Enterobacter* isolates by the mid-1990s, reaching 10% prevalence by 1999. Resistance rates among bacteraemic *Escherichia coli* then remained under 5%, but have since risen to 19% (Figure 1), narrowly exceeding the current rates for *Klebsiella* and *Enterobacter* spp. (Health Protection Agency, data on file). Cephalosporin resistance in *E. coli* is rising too, along with quinolone resistance, mostly owing to the spread of extended-spectrum β-lactamases (ESBLs). These enzymes have been known since 1982 but their types, prevalence and distribution in Europe have changed remarkably since 2003, following similar but earlier shifts in South America and Asia. Before 2003, most ESBLs seen were mutants of the old TEM and SHV penicillinas, largely occurring in *Klebsiella* spp. from specialist units. The new and growing problem is of CTX-M ESBLs, not only in *Klebsiella* spp. but also in *E. coli*. Many infections with CTX-M-positive *E. coli* arise in the community, although occurring in patients with recent exposure to antibiotics or hospitals. From 2% in 1999, the proportion of bacteraemia *E. coli* resistant to oxyimino cephalosporins rose to 9% by 2005, with this rise largely due to the dissemination of CTX-M enzymes. Over three-quarters of the isolates with CTX-M enzymes are multiresistant also to quinolones and aminoglycosides. This growth of multiresistance has practical consequences: *E. coli* is one of the two commonest agents of bacteraemia (*S. aureus* is the other), it is also the commonest agent of urinary infections, and is a component in mixed intra-abdominal infections—all settings where cephalosporins (particularly) and quinolones are standard therapies. Treatment failures associated with ESBLs in *E. coli* and *Klebsiella* spp.
have been linked to increased mortality,\textsuperscript{8} and the spread of these resistances is driving wider use of carbapenems, which do remain active.\textsuperscript{9} Carbapenems previously were reserved agents, but now must be used more widely and, since early effective therapy is critical in severely-ill patients,\textsuperscript{10,11} even empirically for those at high risk of harbouring multiresistant strains.

A shift to greater carbapenem usage inevitably risks greater selection of carbapenem resistance and, to a limited extent—more in \textit{Klebsiella} and \textit{Enterobacter} than \textit{E. coli}—this is happening already, associated with permeability mutations in strains already producing ESBLs or other potent \(\beta\)-lactamases.\textsuperscript{12} Although doubts persist about their 'fitness', such strains are increasingly encountered. Carbapenem resistance is a clearer problem in \textit{Acinetobacter baumannii}, an opportunistic pathogen frequently seen in ventilated patients, burns units and intensive care. In 2000, fewer than 3\% of \textit{A. baumannii} isolates were resistant to carbapenems\textsuperscript{13} and no resistant strain had disseminated among hospitals. By 2006, however, two carbapenemase-producing lineages, the 'SE clone' and the 'OXA-23 clone 1', had each spread to over 35 hospitals around London.\textsuperscript{14} OXA-23 clone 1 is consistently susceptible \textit{in vitro} only to polymyxin, an agent with significant toxicity, and to tigecycline, a novel derivative with unproven efficacy in \textit{Acinetobacter} infections.

A further remarkable rise in fluoroquinolone resistance has occurred in \textit{Neisseria gonorrhoeae}, whereas, previously, infection was standardly cured with a single 250 mg ciprofloxacin tablet.\textsuperscript{15} Until 2000, resistance occurred in fewer than 2\% of UK gonococci, most of them from imported cases. Thereafter, the resistant proportion expanded, first in the heterosexual population and later—more extensively—among male homosexuals.\textsuperscript{16,17} By 2005, the overall rate was 21.7\% and that among gay men was 42.4\%. Long before then, in 2003, first-line ciprofloxacin treatment was abandoned in favour of ceftazidime.

**Factors driving resistance**

These data beg the question—why do some resistances proliferate, whereas others remain exotica for long periods? The answer lies partly in the extent of selection pressure, but this does not explain why CTX-M ESBLs have spread more than TEM and SHV ESBLs, which existed earlier, confer similar resistance and are often encoded by similarly promiscuous plasmids, nor why ciprofloxacin resistance continues to increase among gonococci despite being abandoned as therapy. What often appears critical is the coming together of easy-to-carry resistance, exerting little biological burden, and a fit strain. Many of the resistances discussed here—fluoroquinolone- and cephalosporin-resistant \textit{E. coli} and \textit{Klebsiella} spp., fluoroquinolone-resistant gonococci and carbapenem-resistant \textit{Acinetobacter} spp.—are substantially clonal in the population structure of their host strains.\textsuperscript{14,23,24} Disseminated clones are also responsible for the resistance problems with MRSA,\textsuperscript{25} penicillin-resistant pneumococci\textsuperscript{26} and \textit{Clostridium difficile}.\textsuperscript{27} The features that make some resistant clones particularly successful remain elusive, and it is likely that success arises through multiple favourable combinations of traits, perhaps controlled by global regulator genes, rather than single pathogenicity factors.\textsuperscript{28,29}

Sometimes plasmids succeed, rather than strains: in Poland, those encoding CTX-M-3 \(\beta\)-lactamate have disseminated hugely among hospitals and bacterial species.\textsuperscript{30} The features that make a successful plasmid include 'cheapness to carry', 'useful' resistances and addiction systems.\textsuperscript{31} Addiction systems encode a stable toxin and a complementary, but unstable, antitoxin; the result is that any cell that loses its plasmid is poisoned by a residual toxin. Such a system, which forces the bacterium to adapt to plasmid carriage, has recently been found in the predominant lineage of CTX-M-\(\beta\)-lactamate-producing \textit{E. coli} in the UK.\textsuperscript{32}

In short, the initial evolution of resistance is a fluid process, forever generating random combinations of genes and strains. The subsequent accumulation of resistance reflects the degree of selection pressure and the fitness of the strains that have acquired resistance. It also reflects the new opportunities that arise for pathogens through social and demographic changes and as a result of advances elsewhere in medicine, which expand the pool of vulnerable patients. Resistances succeed in a time and place—they have the zeitgeist of the title—because such combinations of factors favour them. Although much can be done to slow the accumulation of resistance, the idea of mass reversal seems increasingly naive; most of all when resistant bacteria remain competitive even in the absence of continued selection. Rather, the battle is one of containment: minimizing selection and cross-infection, but also re-invigorating antibiotic and (especially) vaccine development as well as enabling faster laboratory recognition of pathogens and their resistances, allowing earlier tailoring of therapy.
Transparency declarations

D. M. L. is employed within the UK public sector and is influenced by HPA and NHS policies and attitudes on prescribing; he has received grants and accepted lecture and conference invites from numerous pharmaceutical companies and holds shares in several, with these holdings amounting to less than 5% of a well-diversified portfolio. He does not believe that his comments in this paper have been materially influenced by these factors, nor that these interests will be materially influenced by his comments in this paper.

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