Minimising antibiotic resistance

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The problems associated with antibiotic resistance have led to several agency and governmental reports since 1998, along with many sets of usage guidelines. These documents stress the desirability of reducing antimicrobial prescribing, which has subsequently fallen in several countries, including the UK. However, the evidence for any contingent reduction in resistance is scanty, and several pathogens—notably Escherichia coli—are becoming markedly more resistant. Thus, rather than being overly optimistic about the benefits of reducing antimicrobial prescriptions, we must also emphasise the use of those antibiotics that prove less prone to select resistance. Furthermore, we must be careful that guidelines are not so narrow as to rail-road prescribing and its contingent selection pressure in single directions—as happened with gonorrhoea—and to consider the likelihood that limited diverse prescribing may have the least detrimental effect upon the resistance ecology. Last, there is a need to re-invigorate antimicrobial development, which has been downgraded by many major pharmaceutical houses.

Introduction

Growing resistance means that once good—and cheap—treatments for infection have been lost, including penicillin and, in hospitals, oxacillins for use against staphylococcal infections; sulphonamides and ampicillin against urinary tract infections; and penicillin and—increasingly—fluoroquinolones versus gonorrhoea.1 Mortality is increased among intensive care patients whose infections are resistant to first-line empirical therapy,2,3 and the presence of bacteria resistant to antibiotics has been associated with increased rates of re-operation, surgical-site infection, and abscess formation in intra-abdominal infection.4 In the specific case of Staphylococcus aureus, outcomes are worse and costs higher for patients with infections due to meticillin-resistant S aureus (MRSA) strains,5 although it is less clear to what extent this differential is due (1) to delay in appropriate therapy for MRSA infections, (2) anti-MRSA glycopeptides being inherently poorer drugs than penicillins, or (3) the traits of particular, locally dominant MRSA clones.

The evidence that antimicrobial prescribing is the main driver of resistance is overwhelming, with critical observations being that acquired resistance is absent from bacteria collected before the antibiotic era, although these may have plasmids resembling the elements that nowadays host resistance genes;7 resistance is most prevalent in those settings (eg, intensive care units)8 and countries (figure 1)9 where antibiotic use is particularly heavy; resistant mutants are sometimes selected in individual patients during therapy, causing clinical failure;10 and new resistance has repeatedly emerged following introduction of new antibiotics, whether in the original target pathogens or via opportunistic species replacement in vulnerable patient groups.11

Since around 1998, concern about resistance has spread from specialist professionals to health-care bureaucrats, politicians, and the public, with numerous agency and governmental reports. These reports vary in emphasis, but can be summarised as advocating less antibiotic use, better use, improved infection control and—less prominently—continued antimicrobial innovation. The major single emphasis has been on reducing prescribing in the community, which accounts for at least 80% of all human antimicrobial use.12 This article reviews the lessons learnt, arguing that early hopes that resistance might be widely tractable to reduced prescribing have been proved optimistic and that we must, for the foreseeable future, depend on a multifaceted approach, discouraging unnecessary usage so as to minimise selection, but also making the best use of present agents and re-stimulating antimicrobial innovation. Infection control is largely outside the scope of this article but is also critical to the management of those resistance types—eg, MRSA—where new evolution is rare and where the major problem is the spread of a few resistant clones among many patients. However, infection control is not a panacea, and is less likely to achieve much useful effect where new resistance arises readily by mutation, or where the ultimately pathogenic organism has long previously colonised the bowel.
The effects of reduced antibiotic prescribing

If usage is the main driver of resistance it seems logical to reduce resistance by reducing usage, and there undoubtedly is scope for sizeable reductions, particularly outside northern Europe. According to data collected by the European Surveillance of Antimicrobial Consumption Group, the average southern European consumes two to four times more antibiotics per year than the average Briton, Dutchman, or Scandinavian,19 without obvious benefit to individual or public health. At least for pneumococci (figure 1) these prescribing differences roughly correlate with differences in the prevalence of resistance. What is less clear is how great a further reduction in usage is achievable without endangering patient safety in those countries (including the UK) where usage is already low, and whether prescribing reductions in countries with heavy usage will reliably achieve reductions in resistance prevalence.

In the UK, a reduction of about 22% in community antibiotic prescribing occurred between 1995 and 2000, with a reduction of over 50% in paediatric prescribing between 1993 and 2003,12 although it is arguable whether these shifts (and similar changes in the USA)24,25 were predicated upon concern about resistance or reflected a lowered incidence of respiratory infection.26 Penicillin-resistance among Streptococcus pneumoniae has also been declining in the UK (figure 2) and, although it is tempting to link this observation to reduced prescribing,27 caution is needed, not least because macrolide resistance in S pneumoniae has remained stable at 11–16%, despite macrolide prescription also being in decline.28 Moreover, there is no evidence for any fall in resistance among the other major respiratory pathogens, Haemophilus influenzae and Moraxella catarrhalis.29 One must also have some concern about claims that reduced community prescribing for lower respiratory tract infections has been associated with increased winter admissions for pneumonia and with increased mortality, although causality is disputed.29,30

Worse, despite reductions in community prescribing, resistance is increasing sharply in Escherichia coli,29 an organism where most infections are community acquired or, even if they arise in hospital, usually involve strains from the patient’s endogenous gut flora. Most notably, resistance to fluoroquinolones in E coli is increasing steadily in England and Wales (figure 3A), as elsewhere in Europe (figure 3B). Additionally, cephalosporin resistance is rising through the spread of CTX-M enzymes, a group of extended-spectrum beta-lactamases, which are increasingly seen in E coli isolates from complicated urinary tract infections, including among community patients (panel 1).29,30 Many CTX-M-positive E coli are resistant not only to cephalosporins but also to other standard treatments for urinary tract infections, including fluoroquinolones and trimethoprim, leaving only the carbapenems, nitrofurantoin, and fosfomycin as reliably active.31 Beside their role in infections, producers are also increasingly seen as part of the commensal gut flora.32,33

In some countries, shifts in the resistance of E coli might be attributable to heavy community fluoroquinolone use, but this is hardly the case in the UK, where quinolones account for less than 10% of all the (relatively low) community antimicrobial usage,13 and where there have been financial and bureaucratic pressures not to prescribe these agents. The emergence of fluoroquinolone-resistant and extended-spectrum beta-lactamase-producing E coli may reflect strains leaking from hospitals or, at least for quinolone resistance, selection in farming and food production. If so, this occurrence would be even more disturbing, since the gut carriage would then imply that the resistant organisms could colonise new hosts even without direct selection pressure. Such organisms will not be easy to displace.

In some cases, reductions in the prescribing of specific antibiotics have been sought, rather than general reductions. Evidence of positive consequences is, again, mixed. Famously, national guidelines to restrict macrolide use for upper respiratory tract infections in Finland led to a two-thirds reduction in consumption, followed, after a 3–4 year lag, by a reduction in the prevalence of macrolide resistance among Streptococcus pyogenes isolates from 19% to 9%,34 largely reflecting the decline of a particular resistant clone.35 The proportion resistant then rose again following a rise in consumption of macrolides, particularly azithromycin, implying causality.36 Less often mentioned is the observation that macrolide resistance in S pneumoniae in Finland continued to rise (albeit from a very low base) throughout the period when macrolide use was diminishing,37 probably because pneumococci—unlike the S pyogenes clone—
were resistant to multiple other antibiotics, which remained selective.

In the UK, concerns about sulphonamide toxicity led to national advice to prescribe trimethoprim rather than co-trimoxazole (trimethoprim-sulfamethoxazole) in most infectious settings, leading to a 97% reduction in community sulphonamide consumption from 1991 to 1999. Nevertheless, the prevalence of sulphonamide resistance in urinary \( E \text{ coli} \) in London rose from 39·2% to 45·8% in the same period,\(^32\) and the proportion of isolates carrying both the \( \text{sul1} \) and \( \text{sul2} \) resistance determinants continues to rise (D Bean, Barts and the London School of Medicine and Dentistry, London, UK, personal communication). Streptomycin resistance, too, seems remarkably stable in \( E \text{ coli} \), despite virtual disuse in human beings.\(^33\) By contrast, resistance to chloramphenicol—another largely abandoned agent—is declining in \( E \text{ coli} \), from 20% in 1990 to 8% in 2004 (D Bean, personal communication). The reasons for these disparities are unclear but it is notable that the genes determining streptomycin and sulphonamide resistances are often linked, perhaps determining their similar behaviour. Retention of these linked resistances may reflect (1) migration of their encoding genes into large multidrug-resistance plasmids\(^34\) that continue to be selected by other agents, or (2) continued sulphonamide and streptomycin use in the livestock industry. Additionally, some small \( \text{sul2} \)-encoding plasmids actually enhance the fitness of the host \( E \text{ coli} \), and may be advantageous even in the absence of antimicrobial selection.\(^14\)

Resistance trends among bacteria from livestock are informative too. The prevalence of vancomycin-resistant enterococci in broiler chickens and (more slowly) pigs declined following the withdrawal of antibiotic growth promoters in Denmark,\(^35\) but wholesale antibiotic withdrawals are rarely feasible in human therapy; moreover vancomycin-resistant enterococci did not completely disappear from Danish flocks even 5 years after the ban, implying that resistance could rapidly be reselected.\(^36\) Equally disturbing is the observation that organic broiler chickens (which are not given antibiotics) mostly carry resistant \( E \text{ coli} \) and increasingly so as they grow older.\(^37\) These data, like those for sulphonamide-resistant \( E \text{ coli} \) in human beings, imply that resistance is not a major burden on bacterial fitness, and further support for this view comes from studies showing that resistant bacteria are now established in wild animal and bird populations, despite the absence of any deliberate prescribing.\(^38,39\)

At a theoretical level, resistance should only diminish under reduced prescribing if resistance exerts a substantial fitness burden through the need to copy additional DNA and to manufacture encoded proteins. In reality, bacteria that have recently acquired resistance often grow more slowly than their parent strains but then tend to undergo compensatory mutations or adaptations, restoring the parental growth rate.\(^40\) Plasmids may also carry “addiction” systems, encoding a stable toxin and an unstable antitoxin; these ensure that any cell that loses its plasmid is poisoned, thus forcing adaptation to plasmid carriage.\(^41\) Moreover, natural variation often generates multiple resistance mechanisms to individual antibiotics and evolution then selects those with the least fitness burden, a factor that may explain why some acquired beta-lactamases have become far more frequent than others and why some of the resistance mutations that are readily selected in laboratory experiments are rarely seen in clinical isolates, notably those that grossly change permeability and surface properties.

**Better prescribing**

Growing evidence argues against the likelihood of achieving major reductions in resistance by reducing...
prescribing, especially as other factors are pushing towards increased prescribing. These factors include a world population growing in numbers, wealth, and health-care expectations, and—most critically—growing numbers of vulnerable individuals with underlying medical problems who experience repeated infections. In addition, the lines between hospitals, care homes, and the community are increasingly blurred, meaning that what were once nosocomial pathogens increasingly leak more widely. Thus, it follows that resistance, rather than being “overcome”, must be managed like a chronic disease.

Reducing unnecessary antibiotic prescribing is undisputedly part of this management, as it should minimise the selection of new resistance. Equally critical, though, is the choice of which antibiotic is used and at what dose and duration, for there are marked differences in selectivity both between, and within, drug classes.

**Selection differences between drug classes**

In recent years the cephalosporins and fluoroquinolones have been used heavily, particularly in hospitals, which now live with the consequences of their particular selectivity. Second-generation and third-generation cephalosporins are associated with the selection of Enterobacteriaceae that are resistant via acquisition of extended-spectrum beta-lactamases (panel 1) and, in the case of Enterobacter spp, Citrobacter spp, Morganella spp, and Serratia spp, with selection of mutants that hyperproduce chromosomal AmpC beta-lactamases. These mutants are frequently selected during therapy, causing clinical failure in individual patients. Third-generation cephalosporins are also widely associated (more so than vancomycin itself) with colonisation and infection by vancomycin-resistant enterococci and Clostridium difficile-associated diarrhoea.

Since quinolone resistance is mostly caused by target (topoisomerase II and IV) mutations that have no effect on other drug classes, one might expect little cross-selectivity. Nevertheless, there is a remarkable association between fluoroquinolone resistance and successful multidrug-resistant strains. This association is apparent for the two predominant epidemic (E)MRSA strains in the UK, EMRSA-15 and EMRSA-16, both of which are resistant to beta-lactams, fluoroquinolones, and macrolides; moreover, there is a striking association between extended-spectrum beta-lactamase production and fluoroquinolone resistance both in nosocomial Klebsiella spp and in CTX-M-positive E coli (panel 1). These associations may reflect the particular success of strains that happen, by chance, to have accumulated multiple resistances while maintaining their fitness; alternately, and speculatively, quinolones may not only select for resistance but may also engender a genetic malleability (eg, by inducing error-prone DNA polymerases) that may facilitate transfer and integration of acquired genes, as well as increasing mutability (panel 2).

A reasonable question to ask is whether aminoglycosides, beta-lactamase inhibitor combinations, or carbapenem would have proved less selective for resistance had they been used as extensively as the cephalosporins and quinolones, or whether they would simply have selected for different resistance problems. Some insight can be gained from studies in which cephalosporins were replaced as standard empirical therapy by other agents, although caution is required as such intervention studies notoriously lack controls and may detect changes that would have occurred anyway. Switches from cephalosporins to beta-lactamase inhibitor combinations have been associated with reduced colonisation and infection by vancomycin-resistant enterococci in several studies, although one study yielded a contrary result. Switches from cephalosporins to piperacillin/tazobactam have also been associated with decreased extended-spectrum beta-lactamase prevalence, and—although piperacillin/tazobactam can select for AmpC-deressed enterobacteriaceae at the ecological (ie, unit) level—it has been much less associated than selection with cephalosporins in individual patients. Switches from cephalosporins to imipenem as standard therapy were associated with reduced extended-spectrum beta-lactamase prevalence, although this gain was partly offset by an increased prevalence of imipenem-resistant...
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Panel 2: Hypermutability and the selection of resistance

Errors—mutations—occur frequently as DNA is replicated, but most are swiftly corrected by DNA mismatch repair systems, such as mutS/mutL.

If these systems are inactivated by mutation, then the mutation rate increases. Such hypermutability is usually harmful but may be advantageous under stressful conditions, such as repeated antibiotic challenge. Thus Oliver and colleagues found that hypermutability was common, along with mutL.

In principle, hypermutability might be selected along with a first resistance, facilitating emergence of further resistances and perhaps also the integration of acquired genes.

This occurrence might explain why resistance accumulates even to drugs, such as fluoroquinolones, where it is extremely difficult to select in vitro, and also the frequent co-presence of mutational quinolone resistance along with acquired resistance to other agents. These hypotheses are, however, speculative, and difficult to test, because of the difficulty of proving the genetic history of an isolate, especially if hypermutability is transitory or inducible.

Pseudomonas spp, a risk that might perhaps have been avoided by using a carbapenem lacking activity against non-fermenters. The table shows one of the more clear-cut studies illustrating the effects of a switch from ceftazidime to piperacillin/tazobactam as empirical treatment for febrile episodes in a haematology unit. Colonisation and infection with vancomycin-resistant enterococci declined after the formulary change, then rose again following a reversion to ceftazidime use, implying causality.

Not all of these associations are readily explicable in terms of direct resistance. Most vancomycin-resistant enterococci are Enterococcus faecium, a species usually resistant to piperacillin/tazobactam as well as to cephalosporins. Likewise, beta-lactamase inhibitor combinations have very variable activity against extended-spectrum beta-lactamase producers, with up to 70% resistant to piperacillin/tazobactam. Perhaps the displacement of resistance reflects poorly understood ecological effects on the collaterally exposed gut flora, which is a reservoir of future opportunistic pathogens. A more general point is whether potent agents should be used first-line or kept in reserve. Standard practice is to use the more potent drugs as reserve agents, but this may be more selective for resistance. In one study, 36% of patients receiving the “conservative” choice of ceftriaxone/metronidazole for intra-abdominal infection developed rectal colonisation with extended-spectrum beta-lactamase producers, whereas none of those given ertapenem did so. It is hard to argue that a prescribing choice that selects extended-spectrum beta-lactamases so strongly is genuinely conservative.

Mutant selectivity within antibiotic classes

Selectivity varies within antibiotic classes, as well as between them. For example, streptomycin has only a single ribosomal binding site, and is compromised by high frequency mutations that alter this site; other aminoglycosides have multiple binding sites and are not compromised so easily. Fourth-generation cephalosporins (eg, cefepime and cefpirome) are more stable to AmpC beta-lactamases than third-generation analogues and so are less selective for AmpC derepressed mutants.

The wisest choice would be to avoid agents that select resistance readily. More generally, if resistance arises by stepwise mutation (as with fluoroquinolones) or via sequential recombinations (as with beta-lactam resistance in S pneumoniae and in gonococci), it seems most likely to be selected by those analogues that begin with only moderate activity, as these drugs are the least likely to be active against all members of an infective population. This argument leads to the concept of a mutant prevention concentration (MPC)—ie, the drug level that inhibits mutants with a first-step resistance. If serum levels are maintained above the MPC for a pharmacodynamically adequate period, then mutational resistance should not emerge (the MPC is not relevant to high-level mutational resistance or to resistance gained via gene transfer). In this context, “pharmacodynamically adequate” means a concentration above the MPC for more than 40% of the dosage interval for beta-lactams and, for quinolones, an area under the inhibitory concentration curve to MPC ratio above 125 against Gram-negative bacteria and above 25 for Gram-positive bacteria.

Quinolones are obvious antibiotics to examine MPC-based arguments, since most resistance to this family is mutational and because there are numerous analogues differing in relative activity. Although ciprofloxacin remains the most active analogue against Gram-negative bacteria, moxifloxacin and gemifloxacin have the best...
activity against *S pneumoniae*, and logic suggests that they should be preferred if fluoroquinolone therapy is sought for respiratory infections. Although this rationale is impeccable, three caveats should be spelt out. First, there is no direct confirmation of the lesser selectivity from clinical experience. Second, these arguments pay no account to collateral selectivity of unabsorbed quinolones on the gut microflora. Third, the in-vitro mutant selectivity experiments (upon which these conclusions depend) are simplistic, since they assume that mutational resistance occurs randomly among strains whereas, in reality, some strains may be primed to develop multiple mutations, owing to lesions in DNA mismatch repair or, perhaps, via the transient induction of error-prone DNA polymerases (panel 2).

**Dose, duration, and emerging resistance**

Unsurprisingly, the selection of mutational resistance is often promoted by prolonged therapy, by infection sites where it is difficult to achieve high drug concentrations, and by under-dosage. These points are well-exemplified by linezolid, a relatively new agent where resistance in target staphylococci and enterococci arises by mutations affecting genes encoding the 23S rRNA target. Staphylococci and enterococci have four to seven copies of these genes, and more than one copy must be altered to confer resistance, meaning that either a double mutation is required or—more probably—a single mutation followed by an internal genetic recombination. Consequently, the emergence of resistance is rare and has mostly been seen in patients receiving more than 2 weeks’ therapy,\(^\text{14}\) in difficult-to-reach sites—eg, a thoracotomy wound with contingent empyema,\(^\text{15}\) and among enterococci in the low-dose arm of a phase III dose/efficacy trial.\(^\text{16}\) In the case of third-generation cephalosporins against enterobacter infections the risk of mutational resistance emerging during therapy is about 20–30% in bacteraemias but under 7% in urinary tract infections,\(^\text{17}\) doubtless because these renally excreted compounds achieve urinary levels above the minimum inhibitory concentrations for most mutants.

These arguments on dose and duration become weaker when single-step mutation confers high-level resistance or where resistance is plasmid-mediated, with its accumulation partly dependent on random transfer events. However, it is generally accepted that the duration of therapy influences the impact on the gut flora, which may act as a reservoir of future opportunistic pathogens.

**Do antibiotic combinations prevent resistance?**

Antibiotic combinations are often proposed on the basis of preventing selection of resistance, as well as for potential synergy. Their value in preventing mutant overgrowth is well established for tuberculosis, leprosy, and HIV infection; elsewhere the evidence is less conclusive. Co-administration of an amino-glycoside (as a thrice-daily regimen) did not militate against the selection of AmpC-derepressed mutants during cephalosporin therapy of enterobacter bacteraemia, although it may have improved clinical outcomes in those cases where cephalosporin resistance was selected.\(^\text{18}\) There is uncertainty as to whether high-dose, once-daily aminoglycoside administration would have been more effective in preventing mutant selection.

**Antibiotic cycling, or diverse usage as firebreaks?**

Antibiotic cycling (rotation) is an old idea receiving renewed interest, more so in the USA than the UK.\(^\text{19}\) For 3 months, say, a unit might use a fluoroquinolone as its preferred empirical therapy, then a cephalosporin for 3 months, then a carbapenem and, last, a beta-lactamase inhibitor combination. Proponents argue that such strategies will militate against the establishment of a stable resistant flora;\(^\text{20}\) sceptics counter that the strategy will select bacteria with multiple resistances, a view supported by mathematical modelling.\(^\text{21}\)

What perhaps is surprising, given the duration of interest, is that there are so few good trials of cycling, and that they have largely been done in intensive-care unit settings with the most complex patients. A meta-analysis identified only nine published implementation studies, with only four suitable for review.\(^\text{22}\) Even these papers were deemed to have methodological flaws and poor standardisation, precluding definitive conclusions but providing little convincing evidence of success. One study in the Netherlands cycled beta-lactams and quinolones in a surgical intensive care unit and achieved 96% compliance\(^\text{23}\) but provided no evidence of resistance reduction and was associated with a 24% increase in antibiotic use, leading the authors to conclude that “Cycling of homogeneous antibiotic exposure is unlikely to control the emergence of Gram-negative antimicrobial resistance in intensive care units”.

Intensive-care units may be the least promising milieu for cycling, owing to the complexity of their patients and their already high prevalence of multidrug resistance. Cycling might well be more effective, say, in gonorrhoea therapy, where a strategy in which clinics had used a 3-monthly rotation of cephalosporins, spectinomycin, and quinolones would have achieved the target of 95% efficacy without creating the conditions whereby ciprofloxacin-resistant strains, once introduced, could spread rapidly, as occurred in UK following a situation where quinolones were used for almost three-quarters of patients.\(^\text{24}\)

Rather than formal antibiotic cycling, some argue for diversity of use as a means of diluting selection.
pressure and preventing the accumulation of particular resistance types. One modelling study concluded that simultaneous heterogeneous antibiotic usage within units should be less selective for resistance than cycling, but, as with cycling, there are no good systematic evaluations. Moreover, although diverse usage may be theoretically desirable, the “open formularies” favoured by some of its proponents must carry a risk of inappropriate usage and of some patients receiving suboptimal treatment. Perhaps the ideal is to seek diversity of rational usage within tight overall limits.

The role of guidelines in the control of resistance
Antibiotic prescribing, like that of other agents, is increasingly driven by guidelines, whether based on local epidemiology, learned-society advice, or (more or less overtly) on the diktat of insurers and health authorities. Any reasonable guidelines should discourage bad usage, including over-long or unnecessary prophylaxis or treatment, or the use of agents likely to be inactive against the pathogens. Antimicrobial guidelines (unlike those for other pharmaceuticals) must also contend with the fact that resistance varies with time and place, sometimes changing very rapidly, and that antimicrobial use has consequences on public as well as individual health. Although there can be little doubt that guidelines prevent much bad therapy, there has to be concern that some are overly prescriptive where debate remains, and a few have had perverse consequences. Three examples illustrate these points.

First, consider acute upper respiratory tract infections in children, where the likely pathogens are *S pneumoniae* and *H influenzae*. If antibiotic treatment is warranted—which is debatable in many cases—the preferred agent is a penicillin. However, if the child is allergic to penicillin, the logical alternative is a macrolide, since tetracyclines and fluoroquinolones are contra-indicated. The available macrolides (unlike those for other pharmaceuticals) have dissimilar profiles in the treatment of *S pneumoniae* but differ in anti-*Haemophilus* activity, with azithromycin the most convincingly active. However, azithromycin has unusual pharmacokinetics, with long serum concentrations and long trailing levels and there are suggestions that this profile is especially selective for resistance. Furthermore, azithromycin costs more than erythromycin. Adding these observations together, it is hard to make any definitive conclusion on which macrolide to prefer.

Second, consider the advice of a cephalosporin plus a macrolide in severe community-acquired pneumonia requiring hospitalisation. This combination covers the likely pathogens (*S pneumoniae*, *H influenzae*, *M catarrhalis*, mycoplasmas, and chlamydiae), but has been associated with the selection of *C difficile* diarrhoea. The combination is also potentially selective for extended-spectrum beta-lactamase producers in the gut flora, which may pose a future infection risk. Might it not be better to use a macrolide in combination with a penicillin or a penicillin/beta-lactamase inhibitor combination, especially where penicillin-resistant pneumococci are infrequent, as in the UK (figure 2)?

Third, consider gonorrhoea. Until recently *Neisseria gonorrhoeae* was exquisitely susceptible to ciprofloxacin, which UK guidelines recommended as a single-dose oral treatment. The convenience and efficacy was undoubted and, by 2000, the drug was used in 74% of gonorrhoea cases. Challenges came from the repeated import of resistant gonococci, principally from southeast Asia, but even as late as 2001, these resistant strains accounted for fewer than 3% of infections. However, in 2002, this proportion jumped to 10%, with local spread of resistant strains among sexual networks. Here, the over-wide adoption of a single guideline created the perfect setting for the spread of the resistant organisms, without the firebreaks that have existed with more diverse prescribing.

The need for new agents
If—as seems likely—the best that can be expected from reduced and better prescribing is an amelioration of present resistance trends, the discovery and development of new antibiotics remains vital. Therefore, the fact that many pharmaceutical companies have quit the field is disturbing. This withdrawal is partly the result of companies merging into larger combines; as a result, the turnover that they receive per product has increased to around $1 billion per annum. For an injectible antibiotic, this turnover translates into 10–12% of the worldwide market—a target unlikely to be achieved if the drug has a narrow spectrum or if it is only to be used against strains resistant to existing agents. Even if wide usage is achieved the drug generates no long-term consumers (unlike, for example, a medication for heart disease, Alzheimer’s disease, or arthritis), and may be compromised by emerging resistance.

Biotechnology companies do seek to develop antibiotics with projected turnovers of much less than $1 billion, but, so far, these mostly depend on venture capital, not sales income. The development of an antibiotic is estimated to cost $500–800 million, with much of this money consumed by phase II/III trials. In principle, this barrier can be overcome by the biotech company joining with a major pharmaceutical company for phase II/III development, but this strategy hits the problem of the declining interest in antibiotics of the big pharmaceutical companies. Alternatively, the biotech company can seek to develop an antibiotic independently, although this may mean that it has to “bet the bank” on one commercial
compound, while shelving long-term programmes that might, ultimately, be more innovative.41
Several promising anti-Gram-positive agents (linezolid, quinupristin/dalfopristin, daptomycin, tigecycline, telavancin, dalbavancin, and ceftobiprole) have been recently launched or are in advanced development, but it is unclear where the next antibiotics will come from. Most disturbingly, there are virtually no innovative anti-Gram-negative agents even in phase I development, least of all any with activity against those nosocomial strains of \textit{Acinetobacter baumannii} and \textit{P. aeruginosa} that have achieved pan-resistance to existing agents.41 The only exception to these generalisations is tigecycline, a novel tetracycline, with activity against \textit{A. baumannii} (as well as Gram-positive bacteria and most Enterobacteriaceae), but not \textit{P. aeruginosa}.

Various proposals have been made on re-invigorating antibiotic development, most recently by Norrby and colleagues41 and the Infectious Diseases Society of America.42 Suggestions include granting tax breaks or patent extensions to companies investing in antibiotic development, and simplification of clinical trial requirements, allowing phase III data to be gathered once a compound is in use, with an income stream being generated.43 If large pharmaceutical houses are to remain interested in antibiotic development and if the area is to open to new entrants, such proposals deserve serious consideration.

Conclusions
The over-riding principle of medicine is “do no harm”, yet, in the case of antibiotics, harm is inevitable, for use (even appropriate usage) selects for resistance, complicating the treatment of future patients. Although reducing antibiotic prescribing seems the logical way to reduce selection pressure, the evidence that resistance can be reduced within the ambit of sustainable reductions in antibiotic prescribing is mixed at best. Moreover, withholding treatment may be associated with serious sequelae in some patients. The most that can be probably hoped for is that the harm of resistance can be mitigated by using antibiotics sparingly, with diverse (rather than cycled) use, and with a bias, at least in hospitals, to those agents (eg, beta-lactamase inhibitor combinations and carbapenems rather than quinolones and cephalosporins) that seemingly cause the least disturbance to the microflora. These aspects should be considered by the authors of guidelines, who must also recognise that rail-roading treatment down overly narrow pathways similarly concentrates the selection pressure. Last, the inexorable conclusion is that, to maintain our ability to fight infection, new antibiotic development must be re-invigorated. And, here, the biggest potential harm is if we—as a society, regulators, and consumers—create a climate in which investment in the field is unattractive.

Conflicts of interest
I have, or manage, shareholdings (directly or as an endurologist) in GlaxoSmithKline, Pfizer, Schering-Plough, AstraZeneca, Micap, and Proteome. I have acted as an invited speaker or on advisory boards in the past 3 years for Wyeth, Pfizer, Merck, AstraZeneca, Leo, Cambridge Antibody, Johnson & Johnson, Baselisa, Pantherix, bioMerieux, Becton Dickinson, and Chiron. I have received research grants/contracts in the past 3 years from Wyeth, Merck, AstraZeneca, Pfizer, Peninsula, Johnson & Johnson, Vicuron, and Pantheirix.

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