Antibiotic stewardship—more education and regulation not more availability?

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Antibiotics are overused across the world by prescription, self-medication or over the counter (OTC) availability. In the UK, the agenda to increase patient choice has stimulated a move towards greater availability of OTC antibiotics. This trend needs to be urgently reviewed and controlled. The Medicines and Healthcare products Regulatory Agency is currently reviewing applications for reclassification of trimethoprim and nitrofurantoin from prescription-only medicines to pharmacy availability or OTC. It is important that anti-infectives do not become more freely available. With the quantity of antibiotic use linked to antibiotic resistance, Society should seek to preserve the use of this irreplaceable resource by education and regulation.

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Patients with infections want to recover quickly and doctors who treat patients with infections want them to improve. The inevitable consequence of this is overuse of antibiotics by prescription and self-medication because most treatment is empirical. In addition, doctors tend to prescribe defensively; if there is a possibility of infection, the logic is often that it is safer to treat. Thus, many doctors and their patients still have the ‘quick fix’ mentality reported by Wise et al.1 over a decade ago that antibiotics can be prescribed for any suspected inflammatory process. However, the rising tide of healthcare-associated infections and antibiotic resistance has promoted a growing realization that the indiscriminate use of antibiotics exerts a detrimental selective pressure on the broader bacterial ecology.2,3 There is an increasing acceptance that Society has a responsibility to manage its precious resources and an increasing awareness that antibiotics are just such a resource. This view was reinforced by the Chief Medical Officer’s report in 2008 that presented a stark message: ‘Every antibiotic expected by a patient, every unnecessary prescription written by a doctor, every uncompleted course of antibiotics, and every inappropriate or unnecessary use in animals or agriculture is potentially signing a death warrant for a future patient.’4 A countermeasure being increasingly advocated is the concept of ‘antibiotic stewardship’ that promotes the use of the right antibiotic, at the right dose, route and duration, for the right bacterial infection at the right time. Continuing education of prescribers and patients, improved diagnostic methods and antibiotic prescribing regulation are all likely to be required to promote this concept. Much antibiotic use is probably inappropriate.1 It has been estimated that up to 50% of human antibiotic use and up to 80% of veterinary antibiotic use could be eliminated without serious consequence. Although the scientific evidence may be complex,5 it is generally accepted that more antibiotic use is associated with greater bacterial resistance. This is borne out by surveys of antibiotic use and resistance across Europe.6,7 Thus, antibiotic use should be restricted to the treatment of infections where the antibiotic will make a real difference. Although the education of prescribers and patients and the development of policies, guidelines and formularies play a vital role in this, a more radical approach is likely to be required. Applications for over the counter (OTC) antibiotics have been increasing, seeking to overturn past acceptance that all antibiotics should be prescription-only medicines (POMs) under the Medicines Act 1968. This has been stimulated, in part, by a trend to increase patient choice and improve access to healthcare, with the result that contradictions have arisen.5,8 Part of the move towards increasing choice for patients and encouraging them to take responsibility for their own healthcare has included widening access to previous POMs [POM to pharmacy (P) reclassification], e.g. in the cases of simvastatin, omeprazole and rantidine. Antimicrobials are being considered for this and this is a serious concern. Such a move to deregulate the status of antibiotics is

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clearly at variance with government initiatives to encourage more appropriate antibiotic use, stimulated by the rise in antibiotic-resistant healthcare-associated infection.\textsuperscript{2,3,9} The Chief Medical Officer’s report announced ‘...moves to widen access to antibiotics without prescription will need to be balanced carefully against the risks of promoting greater resistance’.\textsuperscript{4} In addition, the EU directive is unequivocal: Member States should not allow dispensing of antibiotics without prescription.\textsuperscript{10}

Bodies such as the Specialist Advisory Committee on Antimicrobial Resistance (SACAR), superseded by the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), have been active in advising on antimicrobial resistance and the stewardship of antibiotics.\textsuperscript{11–13} Furthermore, much publicity has been given to campaigns, such as ‘Andbiotic’ and ‘Antibiotics—Don’t wear me out’,\textsuperscript{14} and the first of an annual series of European Antibiotic Awareness Days in November 2008, when the focus was on the appropriate community use of antibiotics and encouraging the public to be more conservative in their use.\textsuperscript{10,15} Department of Health (DH) campaigns such as ‘Winning Ways’ and ‘Saving Lives’ set out strategies for managing infectious diseases and controlling antimicrobial resistance.\textsuperscript{3,9} This approach was given legal endorsement in 2006 with the Code of Practice for the Prevention and Control of Healthcare Associated Infections (part of the Health Act 2006).\textsuperscript{16}

The Medicines and Healthcare products Regulating Agency (MHRA) has been asked in recent years to consider requests from pharmaceutical manufacturers to make certain antibiotics available OTC in pharmacies as P medicines. The MHRA has recently approved changes to the licensing of the antibiotic azithromycin to P status. This change has enabled a systemic antibiotic to be purchased OTC, without consultation with a qualified prescribing clinician. While the benefits of early diagnosis and treatment of chlamydial genital infection are clear, OTC availability of treatment has to be questionable as it fails to address the possibility of co-existing sexually transmitted diseases, contact tracing, prevention and health education, and above all traceability of antibiotic use in connection with antibiotic resistance surveillance. Although this change would now be difficult to rescind, pharmacists dispensing azithromycin in this way could do so with a prescription that was reliably recorded. A prescription is the only way to connect surveillance of resistance to surveillance of antimicrobial use effectively, and resistance to azithromycin amongst gonococci is already a clinical problem.\textsuperscript{17}

An application to change the legal status of trimethoprim was originally made in 2005 and was rejected by the Licensing Authority of the MHRA through its advisory body, the Commission for Human Medicines, following a lengthy review of the issues, the evidence and the concerns raised. At that time the BSAC responded to the consultation and was made aware of the original decision. Last year, following an appeal by the company applying for P status, it was proposed that there should be a phased introduction of trimethoprim availability from pharmacies. The BSAC has been vigorous in its opposition to this proposal, and its concerns are related to the inevitably wider sales and use of antibiotics and the consequent inability to monitor and measure systemic antibiotic usage as is done for prescribed antibiotics. This is the principal reason why the Council of the EU has asked that Members States ensure systemic antibiotics are only available on prescription.\textsuperscript{10} Furthermore if trimethoprim and nitrofurantoin were to be made available OTC then it would inevitably lead to prescribers selecting agents with a more broad-spectrum activity when they were confronted with patients with urinary tract infections (UTIs).

The Royal Pharmaceutical Society of Great Britain had welcomed the changes towards broader availability.\textsuperscript{18} They argued that in terms of symptom management, pharmacists are already familiar with the management of cystitis. OTC trimethoprim would provide an additional treatment option, better access and increased treatment choice for women with cystitis. Pharmacy staff would be provided with appropriate training material prior to any oral antibiotics becoming commercially available OTC. They have pointed out that the proposals to reclassify trimethoprim sought to substitute for prescriptions rather than to increase overall usage. Indeed, a restriction of the pack size to 3 days supply would have limited the amount of antibiotic that is supplied to nationally agreed quantities. They argued that it should not be assumed that changing the legal status to P would necessarily increase usage of these medicines or adversely affect antibiotic resistance.

Given the ever-increasing restrictions on antibiotic use in hospitals, encouraged by the DH, to control resistance and reduce infections due to Clostridium difficile, it did seem paradoxical to propose POM to P reclassification of trimethoprim. In the 3 years since the original consultation, the reasons for keeping systemic antibiotics as POMs have become even more pressing. If the MHRA can reject these proposals they will have averted the potential adverse effects of such a move on the public health of the community, outlined below.\textsuperscript{19}

(i) There is good evidence regarding the link between antibiotic use in the community and the emergence of antimicrobial resistance. Resistance to ampicillin and fluoroquinolones is clearly associated with exposure to these agents.\textsuperscript{6,7} Data from a case–control study show that the risk of an antibiotic-resistant Escherichia coli UTI was significantly associated with a trimethoprim prescription in the preceding month.\textsuperscript{19}
(ii) Selective pressure of using one antibiotic will often select for resistance to other unrelated agents; data from the Cardiff area show that trimethoprim-resistant coliforms are significantly more resistant to second-line treatments such as ciprofloxacin.\textsuperscript{19}
(iii) Selecting resistance in organisms other than those targeted by treatment. Trimethoprim is an oral option for treating various infections caused by methicillin-resistant Staphylococcus aureus (MRSA) and increased trimethoprim use in the community is likely to select for resistance in MRSA.
(iv) The pressing need to ensure prudent use of antimicrobials as one of the vital measures to control and prevent infection with C. difficile and other major public health problems.
(v) Increasing international pressure to promote more conservative antibiotic use in the community as set out in the European Antibiotic Awareness Days.\textsuperscript{10,15}
(vi) Changes in UK policy and practice that have already improved access to antibiotic therapy by prescription. These include the increasing number of independent nurse and pharmacist prescribers and the supply for specific patient groups under Patient Group Directives. This offers patient access to these medicines without having to
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reclassify trimethoprim and nitrofurantoin from POM to P for acute cystitis.

(vii) An increasing role for older antibiotics such as trimethoprim in the treatment of serious infections caused by resistant organisms such as MRSA. In the USA the NIH has recently funded a series of clinical trials that may provide new evidence about the effectiveness of older antibiotics (including trimethoprim) against serious infections.

(viii) Further approval of OTC antibiotics would be in direct contravention of the 2001 Council of the EU recommendation that states should 'implement control and preventative measures to support the prudent use of antimicrobial agents and contribute to limiting the spread of communicable diseases by: (a) restricting systemic antibacterial agents to prescription-only use'.

The MHRA should exclude antibiotics from reclassification. OTC delivery would inevitably result in wider sales and increased use of any reclassified product. At a time when resistance is rising, such use would essentially go unmonitored from a surveillance and indeed safety perspective, despite reassurances to the contrary. It appears that in many cases, approvals of this type are driven commercially and not on the basis of medical need.

It would be a retrograde step for the UK to change the licence of trimethoprim and nitrofurantoin from POM to P availability. Consideration should now be given to changing the OTC licence for azithromycin to pharmacist prescription to ensure adequate surveillance of use. The change in legal status of any systemic antibiotic is at variance with measures by the DH to promote prudent antibiotic use in the community. The BSAC has urged government health ministers to vigorously reject the proposals of licence change, and to act immediately to remove also change.

Antibiotic control needs to go even further. Antibiotic consumption varies hugely across Europe. There is a 3-fold difference in antibiotic consumption between the highest user, France (32.2 defined daily doses (DDDs) per 1000 inhabitants daily), and the lowest, The Netherlands (10.0 DDDs per 1000 inhabitants daily). This cannot be explained by equivalent differences in rates of infection or outcomes and therefore it must be concluded that higher volumes of antibiotic use are inappropriate. Regulation by prescription is no guarantee of prudent use, and overprescribing is clearly linked to resistance. Antimicrobial resistance is generally higher in the Mediterranean countries than in northern Europe. Thus, ampicillin resistance in Spain and Portugal was 54% and 45%, respectively, as compared with 16% and 18% in Sweden and Austria. Corresponding figures for trimethoprim were 25% and 27%, and 9% and 10%, respectively. Fluoroquinolone resistance as measured by nalidixic acid was 27% and 12% in Spain and Portugal, correlating to the highest European consumption.

Self-medication with antibiotics is also a problem in Europe, particularly in southern and eastern countries, and in the USA where several studies have shown considerable self-medication with antibiotics obtained from leftovers from previous courses, at a local pharmacy or outside the country. The most common reasons for self-medication were colds and upper respiratory tract symptoms. This inappropriate use almost certainly contributes to antibiotic resistance.

Antibiotics have probably saved more lives than any other group of drugs. They have been available for almost 70 years and in that time this precious resource has been squandered. Antibiotics have been overused not just in medicine but in agriculture, veterinary medicine and the food industry. Doom-mongers have suggested that we may be approaching a post-antibiotic era in which bacteria are resistant to all available antibiotics. The history of antibiotic resistance has been an arms race between the pharmaceutical scientists developing new agents and the bacteria developing resistance mechanisms against them, and the juggling of chemical compound structures to produce new agents may be almost exhausted.

Antibiotics are the only drugs that do not directly affect the physiology of the recipient patient but instead affect the growth, multiplication and ecology of invading and commensal bacteria. Prescribers of antibiotics have dual, contradictory responsibilities, although they do not often realize it. On the one hand they want to do the best they can for the individual patient they are treating; on the other hand they have a responsibility to future patients and public health to preserve the efficacy of antibiotics and minimize resistance. The former tends to promote overtreatment; the latter is not usually considered. Education could correct this but expectations of prescribers and patients must also change.

In this 200th anniversary of the birth of Charles Darwin, his concepts of chance variation of individuals, natural selection and evolution are as awe-inspiring now as they were shocking to his contemporaries. These are phenomena that are encountered on a daily basis in the field of microbiology and infection. How can the dilemma of optimal treatment for individuals and at the same time reduction in the volume of antibiotic use, thereby reducing the selective pressure on bacterial ecology, be resolved? Probably the only way is to have more, not less, regulation of the use of antibiotics. First there should be rigorous control of agricultural and veterinary antibiotic use for growth promotion and therapy in livestock rearing across the world. Europe has led the way with this. Secondly, it is estimated that ~80% of antibiotic use in humans is in primary care outside hospitals. Government agencies and health commissioning bodies should seek ways to influence the stewardship of antimicrobial use in primary care in a similar way to that which has recently occurred in secondary care. It is likely that antimicrobial use could be reduced substantially without adverse effects on outcomes. In addition, further research should be funded to provide alternative non-antibiotic treatments for common primary problems, e.g. non-antibiotic urinary bacterial inhibitors and symptomatic relief of upper respiratory tract symptoms, and research on the use of older narrow-spectrum antibiotics for new problems such as MRSA infection. Whatever we do, we need to do it soon or, as in the control of carbon emissions to prevent global warming, it could be a case of too little too late.

Transparency declarations

P. D. is Vice President and M. D. is General Secretary of the BSAC. J. C. is a member of ARHAI and chairman of ARHAI’s prescribing subgroup.
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