The urgent need for new antibacterial agents

Richard Wise* on behalf of the BSAC Working Party on The Urgent Need: Regenerating Antibacterial Drug Discovery and Development†

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I find it continually amazing that society as a whole does not recognize the consequences of rising antimicrobial resistance as the threat it most certainly is. This is not for a lack of sustained activity by those who share these concerns. Far from it. Since 1997 there have been a plethora of enquiries, reports and recommendations—many from important bodies in both Europe and North America, yet little meaningful action has materialized. Some might consider this to be rather negative and an overstatement, yet can they point out a concrete outcome to all this activity?

I like to think that the UK has led the way in raising concerns that antibiotic use, especially overuse (in animals as well as man) will hasten the day when these essential agents will lose their efficacy. The Swann Committee† first brought this to our attention in 1969, and in 1998 a House of Lords report starkly stated that antimicrobial resistance was a ‘major threat to public health’. Most recently, the Infectious Diseases Society of America (IDSA)† and the European Union,† among others, have voiced their concerns. In 2009 the WHO called antibiotic resistance one of the three greatest threats to human health, and in 2011 the focus of World Health Day was ‘Combating Antibiotic Resistance’. However, antimicrobial resistance moves on in an inexorable fashion and the prospects for new agents are as bleak as ever. Perhaps it is us, the health professionals, who are at fault, either in the nature of our message, or in approaching the wrong groups who cannot influence outcomes?

The BSAC has changed tack in its report on ‘The Urgent Need’, as outlined in the articles accompanying this one. Rather than restate the concerns surrounding antimicrobial resistance, its surveillance and how it might be contained (or more accurately, how its progress might be slowed), the BSAC adopted a different approach, focusing on the barriers to discovery and development of new technologies that might combat resistance (including new antimicrobial agents) and how these might be overcome. The Working Party of the BSAC examined three areas, namely research, regulation and economics. While recognizing that these areas are not distinct and there is much important overlap, the Working Party was challenged to suggest a practical framework for action. Critically there was an awareness on the part of the Working Party that the BSAC cannot undertake this immense task on its own, and co-operation with others is key.

I do not wish to précis the report here, but rather make some personal comments on what I consider to be a few important areas. In research there is a major concern that international expertise in natural product discovery is being rapidly lost—how long has it been since such an antibacterial compound has been marketed? Overoptimism in genomics and high-throughput screening as the answer to the discovery of new agents in the 1990s would appear to have put back the cause by at least a decade. Research into how to influence the public’s perceptions of the risks confronting them (hence the political response) is also needed. Most certainly the regulatory issues relating to the licensing of new antimicrobials are extremely important. The bureaucrats are risk averse, yet do not take account of the risks to society of their inaction. This would change if political concerns were more loudly voiced. It is my personal opinion that it is changes in the economic field that are most likely to yield results.

We were not the first to expound the economic arguments. Everything the Working Party heard from industry makes me believe that the marketplace must change. A course of antibiotics costs a few pounds or dollars and can save lives. In hospital practice we shudder if the costs rise into the hundreds. The angiogenesis inhibitor bevacizumab (trade name Avastin) is one of the most expensive widely marketed drugs. In 2008 sales generated nearly US$2.7 billion for Genentech, yet it has only modest effects on patient survival in a number of cancers. This is not to say it should not be used, but rather that there should be a rebalancing of risks and, more importantly, benefits. I would suggest that antimicrobials (other than a few antifungals) should be at a higher premium. Antimicrobial development must allow pharmaceutical companies realistic returns on their investment. This is crucial if society is to obtain new agents.

So what actions should the BSAC undertake? The Working Party has suggested a number of short-, medium- and long-term activities. These, realistically, revolve around communication, in its broadest sense, with clinicians and academics, but possibly more importantly, with opinion formers in the UK and further afield. Such a programme of work, which will not be cheap, should include other parties and could usefully include the participation of the pharmaceutical industry.
It goes without saying that such actions are central to the very fundamentals of the BSAC, now celebrating its 40th anniversary, and we the Working Party recommend our report to the BSAC.

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Members of the Working Party
The BSAC Working Party comprised Professor Richard Wise (Chair), Dr Richard Bax (Transcrip Partners LLP, UK), Dr Frances Burke (Eli Lilly, UK), Professor Ian Chopra (University of Leeds), Dr Lloyd Czaplewski (Biota Europe Ltd, UK), Professor Roger Finch (Molecular Medical Sciences, University of Nottingham and Nottingham University Hospitals NHS Trust, Nottingham, UK), Dr David Livermore (Director, Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, London UK), Professor Laura J. V. Piddock (President, BSAC; University of Birmingham, UK) and Tony White (BSAC Council member).

Transparency declarations
D. L. has received conference, speaking and research support from numerous pharmaceutical companies. He holds shares in AstraZeneca, Merck, Pfizer, Dechra, and GlaxoSmithKline, and, as executor, manages further holdings in GlaxoSmithKline and Eco Animal Health. He is an employee of the UK HPA and is a UK taxpayer. R. B. is currently a senior partner at Transcrip partners LLP and works with several large and small pharmaceutical companies in the area of antibiotic development. He is also a non-executive director of Helperby Therapeutics Ltd. R. F. has provided consultative advice to Destiny Pharma, GlaxoSmithKline, Menarini Recherche and Novartis. F. B. is an employee of Eli Lilly and Company Ltd. I. C. is a member of the Scientific Advisory Board of Destiny Pharma Ltd and has recently received research funding from Cubist, Destiny, Galapagos, Leo, Pfizer, Novartis and Novacta. T. W. is an independent consultant, a retired employee and shareholder of GlaxoSmithKline, and in the past 5 years has received financial remuneration for consultancy or presentations from GSK and Chiron/Novartis. The remaining members of the Working Party have none to declare.

References