The control of antibiotic resistance presents a complex and multifaceted challenge. Professional societies, governments and international agencies, including the WHO, have identified a strategy that emphasizes the importance of microbiological surveillance, monitoring antibiotic use, prudent prescribing, education of healthcare professionals and the public and encouraging the development of new drugs and other technologies.

The flow of new classes of antibiotic has substantially declined at a time when resistance rates and new problems have increased significantly. The decline in prescribing rates, the emphasis on the use of generics, the multiple hurdles to be negotiated with licensing authorities and reimbursement agencies are in part responsible. In addition, the failure of genomic-based drug development to show a return on investment has compounded this problem.

With this background, a number of organizations have made efforts to raise these concerns with governments, academia, funding agencies and other relevant parties. The Specialist Advisory Committee on Antimicrobial Resistance recognized the need to address the technology gap. A European Union Intergovernmental Conference was organized on behalf of the UK Department of Health entitled ‘Antibiotic resistance—action to promote new technologies’ in December 2005. The conference gathered together delegates from academia, industry, funding agencies, healthcare management, the European Medicines Evaluation Agency, The European Centre for Disease Prevention and Control, European Directorates and representatives of Member States. Its recommendations have been published.

Keywords: antimicrobials, surveillance, prescribing, education, drug development

Introduction

The UK Specialist Advisory Committee on Antimicrobial Resistance (SACAR) was established in 2001 as a result of parliamentary concerns about the increasing problem of antibiotic resistance and its current and likely future impact on the health of the nation.1 This concern was also echoed in other parts of the world. In the USA, the American Society for Microbiology was the first to identify the growing threats to the safe and effective management of infectious disease.2 The WHO published an influential report in 2000,3 which reviewed the nature of the problem and its likely future impact and made recommendations for its control.

A series of multidisciplinary conferences hosted by various European Union (EU) Member States have addressed specific issues relevant to antibiotic resistance. In particular, the EU conference on the Microbial Threat held in Copenhagen in 1998 established a six-point strategy to be adopted within the EU for controlling resistance (Table 1).4,5

Strategic activity

A number of initiatives within Member States and at the EU level have addressed various aspects of this strategy. Surveillance systems have been established with regular updates (European Antimicrobial Resistance Surveillance System).6 Antibiotic usage data in primary care and, more recently, in hospital care have been captured, standardized and are now published annually (European Surveillance of Antimicrobial Consumption).7 In the UK, a number of prescribing initiatives have been introduced, which include support for guidelines, formulary development and in-use audit with the object of supporting cost-effective and prudent prescribing. In addition, educational campaigns directed at the prescribing healthcare professional and the public have been conducted in several European countries including Belgium, France and the UK.8

Controlling the amount of antibiotic prescribing in primary care has been viewed as an important target for reducing the pressure on the emergence of antibiotic resistance. In the UK,
prescribing has declined by some 25%, especially in relation to community respiratory infections, although the evidence that this has been linked to specific campaigns remains controversial. Prescribing rates in the UK were falling before any formal national campaign. Some argue that it simply reflects a steady and, as yet, unexplained decline in the prevalence of community respiratory infections.9

The importance of high standards of hygiene and housekeeping practices in hospitals has been emphasized by the twin problems of healthcare-associated methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile infection. These have given rise to considerable public concern and an erosion of confidence in the health service. As a result, considerable government and professional effort has been directed at reinforcing good standards of practice and compliance with hand hygiene and housekeeping activities. Standards of hygiene and cleanliness have been established, monitoring systems created, mandatory reporting introduced for MRSA bacteraemia and targets for rate reduction set. Finally, a new Health Act (2006)10 is now in force which underscores these requirements by the force of law.

The technology gap

Antibiotics

Antibiotics have revolutionized the management of infectious disease. Many life-threatening diseases are readily treated, although much minor morbidity associated with community infections has been controlled with a reduction in human suffering and economic benefit to the individual and the nation. Surgery and transplantation medicine have also been rendered very much safer procedures.

The plethora of antibacterial agents developed in the 1950s–70s led to the perception that infectious disease was on the retreat. Indiscriminate and profligate use ensued. The availability of antibiotics for purchase over-the-counter in many countries reinforced the inappropriate use of these drugs.

It is salutary to note that all but two classes of antibacterial drug were discovered more than 40 years ago (Figure 1). The majority of agents are now available in generic form and still remain the ‘work horse’ antibiotics in current use. It is therefore no surprise that as resistance mechanisms become more widely distributed, the clinical utility of these agents is in decline. Antibiotics are unique among therapeutic agents because of this steady erosion of their therapeutic activity as a result of resistance. It therefore follows that there is a requirement for continuous investment into the search for new agents and, in particular, for drugs with novel modes of action.

The switch from screening for natural products as a source of new antibiotics to genomic-based drug discovery and a more targeted approach to drug design have proved a greater challenge than was anticipated, because no genomic-based antimicrobial products have been licensed to date. This lack of return on investment, coupled with the reliance of healthcare systems on generics and the downward pressure on prescribing, has resulted in several pharmaceutical companies disinvesting in antibacterial drug research.11 This has been compounded by mergers and acquisitions to the point where the prospect of new and effective drugs to deal with the rising tide of drug resistance and new pathogenic organisms appears bleak.

Diagnostics

The importance of technology other than antibiotics as part of the strategy to combat antibiotic resistance has lacked emphasis in recent years by those in healthcare, academia and industry. The naive acceptance that infections encountered in hospital and especially in community practice are most effectively managed...
on the basis of clinical assessment and empirical use of antibacterial drugs has perpetuated this perception.

Although greater use of laboratory investigations is made in hospital practice, a minority of infections are microbiologically documented. Even among those that are, only a minority are microbiologically confirmed sufficiently rapidly to influence initial therapeutic choice, thus sustaining a culture of empirical prescribing. There can be few therapeutic areas in medicine where a class of drugs is prescribed in the absence of a specific diagnosis. The current syndromic approach to prescribing is fraught with difficulties in discriminating between antibiotic responsive and non-responsive disease by relying largely on clinical assessment.

The introduction of reliable rapid diagnostic tests at the point of care could greatly support a strategy of prudent prescribing and in turn could transform prescribing practice from one of empiricism to one of greater precision. The degree of sophistication of such rapid tests could range from the simple to the complex. A test that indicates whether bacterial infection is present or absent would have value. A test that is able to indicate the presence or absence of MRSA would be invaluable, not only to support prompt and effective treatment, but also infection control practices. More sophisticated tests that indicate species, resistance markers and virulence factors would also have a role. Finally, host-derived biological markers that indicate the nature and severity of specific infections could also support disease management and treatment schedules.12

Recent initiatives

The Infectious Diseases Society of America was the first to raise concerns over the emerging shortfall of new agents to deal with the emerging threats from resistance.13 A campaign based on the 'Bad Bugs, No Drugs' slogan was launched with a view to gaining widespread professional, public and political support for a package of incentives to encourage new drug development. A more detailed case of need was subsequently published to reinforce this.14 To date, the campaign has failed to gain Congressional support. This campaign was clearly US focused, emphasizing the increasing concerns about the national threat from antibiotic resistance. On the other hand, antibiotic resistance is an international problem and pharmaceutical companies operate in the global arena.

International support for a major strategic initiative was published by the European Society of Clinical Microbiology and Infectious Diseases.15 At the same time, in Sweden, React established an initiative between the Dag Hammarskjöld Foundation, the Swedish Strategic Programme for the Rational use of Antimicrobial agents (STRAMA), and the Division of International Health at Karolinska Institute. React comprised an international network of physicians, microbiologists, researchers, regulatory authorities, pharmaceutical industrialists and others working on the issue of resistance. React published a report entitled 'The Antibiotic Innovation Study', which was based on a series of interviews with key individuals and opinion leaders in industry, academia, finance and the reimbursement authorities with a view to analysing the problems and identifying potential solutions to the current dearth of new drugs.16

**Table 2. Workshop topics discussed at the ‘EU intergovernmental conference on antibiotic resistance: action to promote new technologies’**

<table>
<thead>
<tr>
<th>Workshop</th>
<th>Topic</th>
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<tbody>
<tr>
<td>1</td>
<td>‘Linking surveillance to identify unmet needs and define the research agenda’</td>
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<tr>
<td>2</td>
<td>‘Obstacles to greater acceptance of new technologies in healthcare’</td>
</tr>
<tr>
<td>3</td>
<td>‘The commercial reality of new drugs, vaccines and diagnostics innovation—which medical needs will be met and which will not and why?’</td>
</tr>
<tr>
<td>4</td>
<td>‘European regulatory opportunities—facilitating innovation without compromising safety’</td>
</tr>
<tr>
<td>5</td>
<td>‘Leadership, strategy and policies to remove barriers to innovation and create a sustainable environment for technology-based solutions’</td>
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**SACAR’s response to the technology gap**

SACAR organized a European Union Intergovernmental Conference on behalf of the UK Department of Health which was sponsored by the BSAC. This was held in Birmingham, UK, in December 2005.17 The programme was designed to include a series of keynote presentations which identified the major issues. There followed a set of five workshops, each dealing with a specific topic (Table 2), which were discussed using a series of prepared questions. Each workshop brought its recommendations to the plenary for further discussion and endorsement. Delegates were invited and drawn from academia, industry, funding agencies, healthcare management, the European Medicines Evaluation Agency, the European Centre for Disease Prevention and Control, European Directorates and representatives of EU governments. The key conclusions are summarized in Table 3, although more specific recommendations were made in relation to the series of questions addressed by each workshop.17

**Table 3. EU intergovernmental conference: key conclusions and recommendations**

- The need for new healthcare technologies is endorsed
- Better surveillance of resistance that links outcome and economic impact
- New funding models need to be identified, especially for Phase I studies
- New near-patient diagnostics should be developed to sustain the effectiveness of existing antibiotics
- Healthcare systems need to recognize their technology gaps and demonstrate greater acceptance to pay more for innovation
- Regulatory processes need to be harmonized, streamlined and supportive of earlier licensing
- Leaders, champions and advocates are essential to articulate the need for new technologies to the public and the EU
Concluding remarks

There are few dissenting voices about the concerns that antibiotic resistance holds for the future health of mankind. The speed with which resistance is currently escalating among community, as well as hospital microorganisms, is extremely worrisome. Nonetheless, a strategy to contain resistance through technology innovation, prudent prescribing, high standards of hygiene, environmental cleanliness, education and training in order to promote the useful life of existing therapies is not unrealistic. However, it will require leadership and sustained international collaboration from governments, industry, academia, finance agencies and healthcare systems to support the multifaceted strategy which is necessary. To do nothing is not an option.

Transparency declarations

R.F. is a Non-Executive Member and Deputy Chair of the UK Department of Health Specialist Advisory Committee on Antibiotic Resistance as well as Education Secretary to the British Society for Antimicrobial Chemotherapy. In addition, he holds consultancy agreements with Astellas, Bayer, Chiron, Cubist, GlaxoSmithKline, Mayne Pharma, Novartis and Prolysis. The content of this article does not contain any reference to the products or research activities of these companies. This information is provided solely in the interests of transparency.

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