# The Urgent Need
# Regenerating antibacterial drug discovery development

## Report of the British Society for Antimicrobial Chemotherapy Initiative

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**The Urgent Need: regenerating antibacterial drug discovery development**

"*Antibiotic resistance - one of the three greatest threats to human health*", World Health Organisation, 2009

## INTRODUCTION

The British Society for Antimicrobial Chemotherapy is gravely concerned that the relentless rise in antibiotic resistance, occurring at a time when pharmaceutical companies are disinvesting in the discovery and development of antibacterial agents, will have severe and harmful effects on global health and our ability to treat infections in hospitals and the community. The antibiotic pipeline is almost empty, yet the need for new antibiotics to treat the increasing number of drug resistant infections continues to rise.

The models by which antibacterial agents are discovered and subsequently brought to market no longer appear to be as effective as they once were. The magnitude of the problem faced is aptly demonstrated by the IDSA 2004 Report *Bad Bugs, No Drugs*, which reports on sixteen new antibacterial agents being approved and brought to market between 1983-1987, compared with the estimate that between only two and four new antibacterial agents will reach market between 2008-2012. It is by no means clear if even these will address the current clinical issues.

The Urgent Need initiative was established in response to these concerns, to identify barriers discouraging participation in antibacterial drug discovery research, and to consider what opportunities exist to re-stimulate interest in the field, possibly through public / private partnership initiatives.

Our initiative is not unique, but it is an important part of a growing international movement that recognizes the need for, and demands, action before the global medical community is faced with the unthinkable – a post-antibiotic era where the treatment of infections, from the common to complex is no longer possible.

Looking at the three major components required to bring antibacterial agents to market – research, regulation and economics – this report records the discussions held at three expert evidence sessions. It does not seek simply to reiterate problems that have been rehearsed, recorded and reported so many times before, but to identify practical solutions that can be developed, applied and implemented, using existing systems for research, regulation and pricing,

In summary, we aim to offer suggested frameworks for action that if taken forward with imagination and commitment can and will make a real difference.

**Professor Richard Wise**
**Chair, The Urgent Need Initiative**

**Professor Laura JV Piddock**
**President, BSAC**

## EXECUTIVE SUMMARY

The developed world has seen an explosion in the incidence and reporting of multi-resistant drug infections both in hospital and community settings. MRSA, *Clostridium difficile* and most recently Enterobacteriaceae with NDM-1 enzyme feature regularly and prominently in the media. Patient pressure groups demand their eradication, governments set targets for their control and reduction, high-profile deep clean campaigns have been undertaken as part of increasing efforts to control their spread, and a plethora of health interventions have been researched, developed and introduced in a bid to improve surveillance, monitor, record and drive down infection rates.

The concerns are valid and the concerted actions from public, professional and political quarters are to be applauded. Their impact should not be undervalued. However, neither should they mask the critical need to discover, develop and bring to market new agents to combat resistance and treat existing and emerging multi-drug resistant infections. The number of new agents in the pipeline is at its lowest ebb since the early 1940s when penicillin was developed and launched and there is an urgent need for the innovative regeneration of drug discovery and development markets. It is a story that rarely attracts press interest, yet the consequences of failure would be catastrophic.

Without new antibiotics, medicine will change beyond recognition. Nowadays, abdominal, heart and transplant surgeries have become routine, whilst ever-more-targeted and sophisticated chemotherapy regimens have dramatically improved cancer survival rates, but often leave the patient very vulnerable to infection. None of this would be possible without effective antimicrobial treatments. The re-emergence of diseases such as tuberculosis, which were all but eradicated, poses significant threats and treatment challenges in both developed and developing countries, as does the emergence of multi-resistant gonorrhoea.

This call to action is real, and action is needed now.

Looking at the market place for antibacterial discovery and development, there are several areas that require attention, each with differing but interlinked interests.

### Public perception

In promoting this cause we begin from an overall position of disadvantage. Patients and their families see it as a right to expect and receive timely and effective treatment. Public education campaigns have raised awareness of the need to use antibiotics appropriately but there is little, if any, evidence to suggest that the general public is aware of the dilemma facing antibiotic research and development. The public are unlikely to be aware that the problem exists, let alone its scale. It is even more unlikely that they have given any thought to what might happen if the market fails. It is incumbent on the infection community to work together to influence public opinion. We need to engage with organisations and bodies such as Cancer Research and the Kidney Alliance, which have successfully forwarded their cause through capturing and maintaining public interest. There is a need to work with such allied professional specialist groups to raise awareness, highlight the consequences of inaction, mobilise support and bring pressure to bear on governments, regulators and decision makers to engage and support initiatives that will regenerate the market.

### Failure of discovery

The science of antibiotic discovery is especially difficult and the failure to bring new antibacterials to the market partly reflects a failure of discovery; during the past 30 years only two new classes of antibiotics have been developed that reached the clinic. In particular, potent commercialisable compounds with anti-Gram negative

activity have not been found and, although in the past decade compounds with anti-Gram positive activity have been developed several of these were discovered decades earlier – examples include daptomycin and oritavancin.

The failure of discovery can be attributed to the combined effects of several interacting factors:

- The challenge posed by the fact that an anti-infective, unlike any other pharmaceutical, needs (i) to have multiple targets in terms of bacterial species and (ii) to work in multiple different infection types, arising in different body compartments.

- The genuine rarity of drug classes that can effectively permeate Gram negative bacteria and evade their endogenous efflux. This challenge is particularly great for *Acinetobacter* spp. and *P. aeruginosa*. This challenge is compounded if one further accepts that any single-target drug is likely to be vulnerable to mutational target-mediated resistance and that a desirable drug therefore should have multiple targets –as do the $\beta$-lactams, aminoglycosides and fluoroquinolones.

- Over-optimism in the 1990s for genomics, which identified targets but not compounds and, even where compounds were found, underestimated the challenge of getting these molecules into bacteria or preventing their efflux. The corollary of this shift was an abandonment of tried-and-trusted methods of antibacterial discovery, notably natural product screening.

- Mergers among big pharma, which reduced the number and diversity of the teams seeking to discover new antibacterials, simultaneously with a reduction of academic investment in the field.

The research report explores and addresses the above issues in detail.

**Failure to bring agents to market**

The barriers in bringing new anti-infectives to market hinge primarily on the lack of return on investment. Antibiotics, unlike drugs that treat the symptoms of chronic disease, offer a relatively poor return on investment. Put simply, the patient takes a heart drug for life but only takes an antibiotic for a week or thereabouts; moreover, prescribing a new antibiotic is likely to be restricted for fear it will select resistance. Estimates of the financial return ('Net present value, NPV') for antibacterials have been calculated as being lower than those for vaccines, or therapeutics used to treat oncology, CNS and musculoskeletal diseases. Only oral contraceptives offer a poorer return. There are many market failures and there is a high cost of antibiotic resistance which is not reflected in the actual cost of the drugs.

Development of narrow-spectrum agents, the push for prudent antibiotic prescribing to reduce resistance rates, and the policy of preserving new agents as last-line treatment options do little to encourage industry to invest. There needs to be a paradigm shift in how antibiotics are perceived and priced to ensure that return on investment is met and interest in the development of agents regenerated.

The lack of attraction of anti-infective development is compounded by the complexity and high cost of Phase III clinical trials. This process is a particular deterrent for smaller biotech companies who might otherwise invest in this area but who are unlikely to be able to raise sufficient funds for Phase III clinical trials.

What is more, whilst there are many patients with antibiotic resistant infections, there are many more with antibiotic-susceptible ones, in whom cheap generic antibiotics can be used. These command a low overall price, and there is no requirement for their producers to evaluate their efficacy against current products; nor

were they ever evaluated in clinical trials of the standards, size and statistical quality demanded for new agents. The efficacy of some generics has been questioned, and the ability of the large volume of generic antibiotic use to select for resistance is not routinely documented. Policy directives instructing the use of generics over branded products, further compounds the perception that antibiotics should be low cost.

The research, regulatory and economics reports each encompass commentaries on the economic barriers to bringing new anti-infective agents to market.

**The regulatory environment**

Licensing and regulation exists to support the public health agenda and ensure the safety of patients. These objectives cannot and should not be compromised. However, new ways of working within existing systems are needed.

By definition, the regulatory process is risk averse, and this can be particularly onerous for the approval of anti-infective agents. The main difficulties lie in the increasing levels of bureaucracy, and lack of clarity, within the regulatory framework and global differentiation in the clinical trials process. Lack of international harmonization, continual changes to processes, and ineffective pathways for dialogue between organizations, industry and regulators are all significant deterrents to the research and development of new anti-infective agents. Whilst there is evidence of progress in clinical trial design, much more work is needed, with a particular need to develop improved diagnostic tests swiftly to identify pathogens and their resistance, and the application of pharmacokinetic/pharmacodynamics data.

The regulatory report highlights what options currently exist to move regulation forward. It highlights options for adapting and utilizing the accelerated approval processes that have been successfully used in other therapeutic areas.

**Evaluating societal and human cost**

Influencing governments will require more than emotive words and doomsday scenarios. It will also require more than statements of fact on the dwindling antibiotic pipeline and the difficulties faced in the mobilization and funding of research, or on making commercial antibiotic development more financially viable.

As a profession we need to evidence the economic and human costs of resistance and the potential costs of inaction. The economics report outlines recent initiatives and current models that have been or might be used to determine this. Each initiative has its merits, but it is clear that none are able to comprehensively quantify the economic burden or human cost of resistance or rise in untreatable infections. There is an urgent need for the development of models that help us to do so.

**Recommendations**

The reports of the three expert evidence days – research, regulatory and economics – each detail options for consideration and action. Our recommendations take the form of a proposed agenda for action, comprising a number of legacy activities, including a call to establish an All Party Parliamentary Group Select Committee on Antibacterial Drug Discovery and Development that will encompass some or all of these options.

# COPIES OF THE FULL REPORT AND PROPOSED AGENDA FOR ACTION WILL BE AVAILABLE AT THE MEETING

**Working Party Membership**

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|---|---|
| Professor Richard Wise | Chair |
| Dr Richard Bax | Transcrip Partners LLP, UK |
| Dr Frances Burke | Eli Lilly, UK |
| Dr Lloyd Czaplewski | Biota Europe Ltd |
| Professor Ian Chopra | University of Leeds, Leeds |
| Professor Roger Finch | Chair, Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection and XX hospital |
| Professor David Livermore | Health Protection Agency, London |
| Professor Laura Piddock | President, British Society for Antimicrobial Chemotherapy and University of Birmingham |
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