

LESSONS TO BE LEARNT FROM PHARMA ABOUT DISCOVERY AND DEVELOPMENT OF NEW ANTIBACTERIAL DRUGS



A summary of an interactive one-day symposium organised by Antibiotic Action and held at the Wellcome Trust, London, UK on 21 May 2013

**ANTIBIOTIC
ACTION**

Preface

The rise of antibiotic resistance has been described by the World Health Organisation as one of the greatest threats to humankind. In January 2013, the World Economic Forum indicated that the threat was so great that it should be added to the Global Risks Register. And in her annual report in March 2013, the UK's Chief Medical Officer, Dame Sally Davies, described antibiotic resistance as a 'ticking time bomb'.

It is widely recognised that we are nearing an apocalyptic scenario in which people undergoing commonplace medical treatments including surgery die of routine infections because no effective antibiotics are available. Despite increasingly vociferous warnings from public health professionals and scientists, we are no closer to defusing this time bomb than we were a decade ago.

Like all complex problems, there is unlikely to be one single solution to the threat of drug-resistant bacteria. Market incentivisation may generate sufficient economic leverage to reinvigorate industrial antibiotic R&D, though in the current climate this seems unlikely. Enhanced stewardship of the dwindling supplies of antibiotics in our medicine chest is absolutely essential. But for some bacterial infections, such as those caused by multidrug-resistant Gram-negative bacteria, few therapeutic options remain. We must also boost the discovery and development of new antibiotics, to supplement and supersede medicines that have lost their power to control infection and repopulate the developmental pipeline.

The academic and medical communities have shown enthusiasm to support these goals. However, the path from laboratory to clinic is long, complex and expensive. Given the urgency of the challenge and inevitable financial constraints, the chances of successful antibiotic development need to be maximised by learning lessons from past successes and failures, and by drawing on the experience of those in 'big pharma' who have a track record in antibiotic discovery, research and development.

This was the aim of the 'Lessons to be Learnt' interactive one-day symposium, organised by Antibiotic Action and supported by the British Society for Antimicrobial Chemotherapy (BSAC), the Biotechnology and Biological Sciences Research Council (BBSRC), the Medical Research Council (MRC) and the Wellcome Trust. The interdisciplinary workshop brought together key individuals from academia, the biotech and pharmaceutical sectors, and clinical practice to discuss why antibiotic development has stalled and what can be done to restart it.

Laura J V Piddock

Professor of Microbiology and Deputy Director of the Institute of Microbiology and Infection, University of Birmingham, UK.
Director, Antibiotic Action, and BSAC Chair in Public Engagement

Copies of this report can be downloaded from www.antibiotic-action.com

Text: Ian Jones, Jinja Publishing Ltd
Design: Tess Wood (www.tesswood.com)
Cover: Antibiotic pills: James King-Holmes/SPL

Antibiotic Action is supported by the British Society for Antimicrobial Chemotherapy (www.bsac.org.uk)

Executive summary

There is an urgent need for new antibiotics, particularly to tackle the rise of antibiotic-resistant bacteria.

New antibiotic development has slowed alarmingly in recent decades, and the antibiotic development pipeline is poorly stocked. This lack of activity reflects 'market failure' – pharmaceutical companies have retreated from antibiotic development as the risk–reward ratio has been considered unattractive.

Action is required in a range of areas to counter antibiotic resistance, for example ensuring existing drugs are used appropriately in human and veterinary medicine. Innovative financial mechanisms may also be able to encourage greater industry investment. However, to pump-prime the antibiotic pipeline, there is also an urgent need to boost the discovery and early development of antibiotics. Academia has a pivotal role to play in this process.

Given limited resources, it is essential that this work is productive and scientifically rigorous, and that academic researchers learn from the experience of industry researchers, in the biotech and pharmaceutical sectors, who have had practical experience of antibiotic discovery and development.

Product-focused research requires a different mindset to conventional microbiological research, with the practicalities of application considered at the beginning. As well as target identification, rigorous target validation is required to minimise the risk of later-stage failure. Importantly, the potential for resistance to develop must be analysed thoroughly – if resistance readily arises in laboratory studies, a therapeutic approach is unlikely to succeed in the clinic.

Academic researchers also have important roles to play in elucidating aspects of bacterial physiology relevant not only to antibiotic discovery but also to antibiotic use, such as the biology of the bacterial cell wall, entry and efflux systems (particularly of Gram-negative bacteria), and mechanisms of resistance. A prioritised list of key questions would be valuable to guide such work.

Building antibiotic development expertise in academia would be advantageous. Skills development courses may be beneficial, but there is also a need to draw on industry expertise and to foster greater collaboration between academia, the biotech sector and the pharmaceutical industry.

Cross-sector consortia may be one approach, though there may be other ways for groups to work together in precompetitive space or under open innovation principles, if intellectual property issues can be resolved. If such approaches are not successful, more adventurous solutions may be required, such as entirely public sector-led initiatives.

A renewed focus on antibacterial drug discovery and early translation needs to be accompanied by action in other areas, including advocacy, political debate and public education, to ensure that the profound challenge of antibiotic resistance is widely recognised and action prioritised.

Introduction

Antibiotics have saved countless millions of lives. From being the major cause of death before the 1930s, bacterial infections in developed countries can now largely be controlled. However, bacteria are resilient foes. Drug resistance was noticed almost immediately after antibiotics began to be used in the late 1940s and 1950s, and now affects all major classes of antibiotic.

Since many of the original antibiotics were natural products, drug resistance genes existed before the antibiotic era. Widespread use of antibiotics selected for pre-existing drug-tolerant or drug-resistant variants, or provided an environment in which new mutants had a marked survival advantage. The promiscuous exchange of mobile genetic elements has also provided a way in which drug resistance genes can spread, even between distantly related bacteria.

Antibiotic resistance has therefore driven an arms race between humans and pathogenic bacteria. In what is now looking like a golden age of antibiotic development, through the 1960s and 1970s humans dominated this struggle, generating a diverse medicine chest of antibiotics.

From the 1980s, however, the tide has been turning and bacteria may now be gaining the upper hand. The pace of antibiotic development has slowed alarmingly. No new class of antibiotic was launched between 1980 and 2000, and even recent products have been based on discoveries made decades ago. Industry has largely abandoned new antibiotic development, and the drug pipeline is poorly stocked, even as the need becomes more urgent.

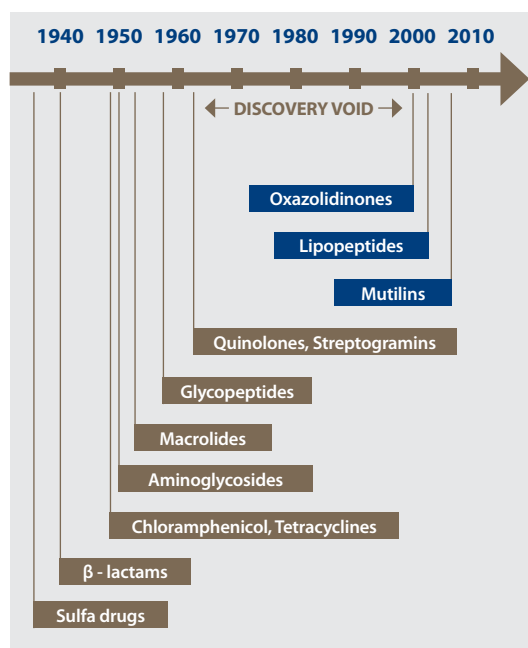
Drug resistance is an issue for all bacterial pathogens. Methicillin-resistant *Staphylococcus aureus* (MRSA) has perhaps captured greatest attention, but intensive efforts at infection control have lessened its impact in healthcare facilities. Nevertheless, it remains a persistent threat and is now commonly found in the community as well as in hospitals. Control of *Clostridium difficile* in clinical environments also requires constant vigilance, as does the prevalence of antibiotic-resistant *Streptococcus pneumoniae* infections in children.

Globally, multidrug-resistant tuberculosis is a huge threat, and outbreaks of highly virulent 'extremely drug-resistant' (XDR-TB) strains have alarmingly high mortality. Recent years, however, have seen concerns growing about drug-resistant Enterobacteriaceae, including *E. coli*, *Klebsiella* and *Salmonella*, and other Gram-negative bacteria such as the opportunistic pathogens *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, as well as *Neisseria gonorrhoeae*.

Drug-resistant strains force physicians to turn to 'second-line' antibiotics, generally more expensive and with a wider range of side-effects. Yet strains are also developing resistance to these back-ups, often leaving doctors with few options to treat infections. As treatment failures of multidrug-resistant infections have already been reported, it is not fanciful to raise the spectre of widespread genuinely untreatable bacterial infections in the near future.

Against this background, the 'Lessons to be Learnt' symposium brought together a range of stakeholders with an interest in the discovery and development of new antibiotics – microbiologists and chemists, including those identifying new therapeutic leads, scientists from biotech companies where much new antibiotic development is taking place, industry researchers with first-hand experience of antibiotic development, and clinicians who face the daily challenge of drug-resistant infections. The aim was to discuss how the antibiotic pipeline could be pump-primed with new leads and antibiotic development accelerated, by examining what worked well in the past and, equally importantly, what did not.

Between 1962 and 2000, no major classes of antibiotics were introduced. No registered classes of antibiotics were discovered after 1987. (Adapted from Fischbach MA, Walsh CT. Antibiotics for emerging pathogens. *Science*. 2009;325:1089-93.)



Antibiotic translation

During the golden age of antibiotic development, agents were mostly discovered serendipitously, by screening of natural products, or were developed by modification of existing agents. Industry had well-established drug discovery and development programmes to deliver effective antibiotics, even if it was not always clear how they worked.

However, from the 1970s onwards, the previously plentiful supply of new antibiotics began to dry up. With productivity in decline, industry looked to new approaches to boost the supply of antibiotics. Indeed, new technologies promised to offer an alternative to the serendipity-based approaches of the past. Particularly through genetics and genomics-based approaches, specific new targets became easier to identify, while 'rational' drug design and synthetic chemical libraries emerged as alternatives to high-throughput screening of natural products.

Unfortunately, these new approaches have not led to a surge in new antibiotics. Possibly early successes masked how difficult antibiotic development actually is. As with all pharmaceuticals, new agents need to show efficacy as well as safety – they need to kill bacteria but not people. But they must also be robust to the development of resistance. Efficacious compounds may in practice be worthless because bacteria rapidly develop tolerance.

The new model of discovery, based on bacterial genomics, has not proven successful at delivering agents fulfilling all three criteria. Furthermore, by concentrating on drug–target interactions, this model often overlooked the whole-cell context. A chemical may be a good inhibitor but be poor at entering or remaining within a bacterial cell.

At the same time, changes in the regulatory requirements to demonstrate safety and efficacy with lack of clear guidance on the expectations required for a licence have arguably made it more difficult to gain approval for new antibiotics, adding to the risk of failure and to the costs of R&D. It is, for example, debatable whether many currently used agents would pass the more stringent criteria used today. While regulatory authorities are naturally focused on patient safety, there is a concern that their policies and decision-making act as a disincentive to antibiotic development just when new drugs are most in demand. In addition, the need for new agents to be at least as good as existing agents – the 'better than the Beatles' syndrome – is a further impediment, when the diversity of agents is as important as efficacy if we are to keep pace with the development of resistance.

International differences in regulatory regimes are also a source of frustration, adding to development time and costs. A more joined-up global approach and shared assessment criteria would help to accelerate antibiotic development.

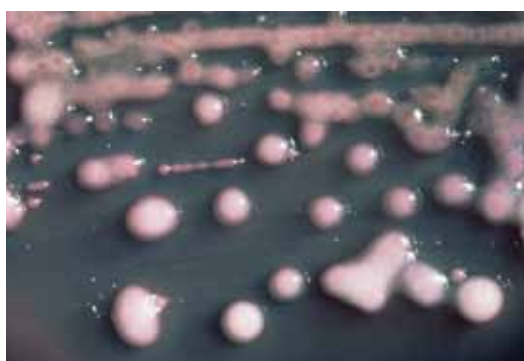
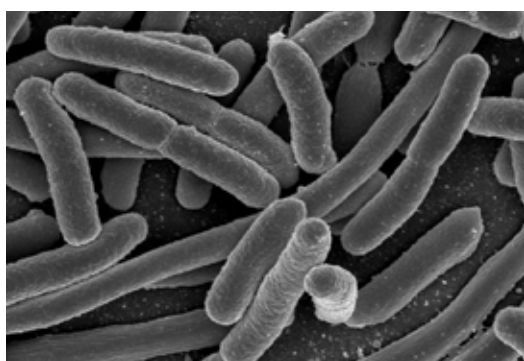
A combination of these factors, plus, critically, the expectation that antibiotics should be cheap, led industry to move away from antibiotic development. Part of the resulting gap has been taken up by smaller companies in the biotech sector, often spin-outs from pharmaceutical companies. Yet it is challenging for such companies to support the full commercial development of new drugs through to the marketplace.

A further significant issue is the desirability of combination therapies. Several infectious diseases, particularly HIV/AIDS, TB and malaria, are routinely treated with multiple drugs against different targets. This reduces the likelihood that drug resistance will develop – organisms tolerating one drug are eliminated by the others, and it is less unlikely that that one organism will simultaneously develop high-level resistance to several agents.

Antibiotics are sometimes used together (e.g. co-trimoxazole), but this is usually to broaden their efficacy rather than as combination therapy of drugs acting on different pathways. With novel agents in short supply, developing combination therapies is particularly challenging – as well as an estimated 1 in 1000 success rate for each individual agent, in theory the combination would have to be tested together to assess pharmacodynamic compatibility and to satisfy regulatory authorities. In the long term, it is likely that combination therapies will be essential, but in the short term alternative strategies will be required.

Top: *E. coli* (Rocky Mountain Laboratories, NIAID, NIH).

Below: *Klebsiella pneumoniae* (CDC).



Targets: The need for rigour

The starting point for antibiotic development remains specific bacterial targets. A good target usually has the following properties:

- It is not present in the host
- It is essential to the organism's survival.

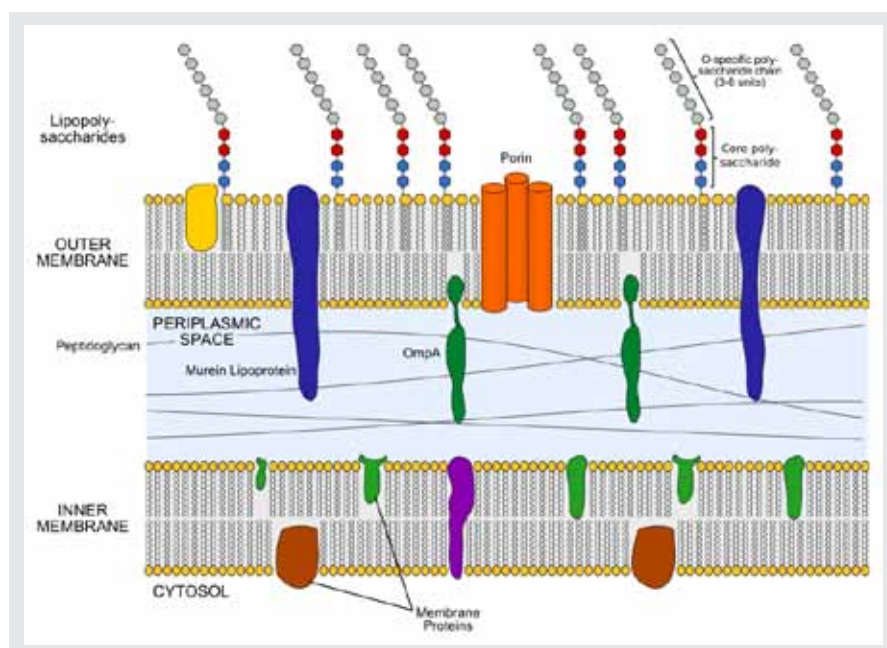
However, it is now clear that these criteria are necessary but far from sufficient, and a more rigorous assessment of potential targets is needed. Of profound importance is the likelihood that an organism will be able to evolve resistance to an inhibitor. This may occur by mutation of the target, negating the impact of the antibiotic, or by compensatory mutations in other genes. The latter may lead to shifts in metabolic pathways that enable the therapeutic block to be bypassed, or an organism may develop or acquire a way to disable an antibiotic (for example by breaking it down), prevent its entry or eject it from the cell.

These factors need to be rigorously explored early in discovery, research and development. If resistance appears to develop relatively easily in the laboratory, then it is unlikely that a therapy is going to be successful. It has been argued that organisms evolve resistance in laboratory settings at the expense of 'fitness', and are therefore likely to be outcompeted in the real world. However, recent experience suggests that supposedly 'unfit' bacteria can acquire compensatory mutations that enable them to overcome the impact of resistance. Hence resistance in the laboratory is likely to be mirrored in the clinic. Although research can be carried out to determine how to minimise the emergence of resistance during treatment, it may be necessary to terminate development of a drug.

A further factor that needs to be considered is the 'druggability' of targets. Genetic studies exploring essential bacterial genes may identify good targets, but if the corresponding protein is difficult to inhibit with chemical agents, in practice a successful therapy is unlikely to be developed. Although general druggability principles have been established, the extent to which they apply to antibiotic development is unclear. In practice, key issues such as the flexibility of binding pockets – a target may be able to tolerate multiple mutational changes and maintain its essential bacterial role while circumventing drug inhibition – need to be extensively studied experimentally.

Characterisation of new targets can be carried out in academia, but academic research can also contribute by elucidating aspects of bacterial biology relevant to antibiotic development.

The cell wall of Gram-negative bacteria
(Jeff Dahl).



Good examples are the uptake and efflux systems of Gram-negative bacteria, which present a particular challenge to target-based drug discovery. Intracellular targets, for example, are protected by a permeability barrier – the inner and outer membranes and the cell wall – and getting an antibiotic into the cell is difficult. Piggybacking uptake systems runs the risk that resistance will develop by changes to transporter binding. A better understanding of the structure and function of the cell wall of Gram-negative bacteria, including the lipopolysaccharide, could underpin novel ways to deliver drugs into bacterial cells.

Furthermore, bacteria also possess efflux mechanisms that eject antibiotics. Genes for such efflux systems are usually encoded on the bacterial chromosome, but can be present on plasmids that are transferred between bacteria. An understanding of efflux systems, particularly of Gram-negative bacteria, is essential for antibiotic development, as many compounds have failed due to rapid export coupled with poor entry.

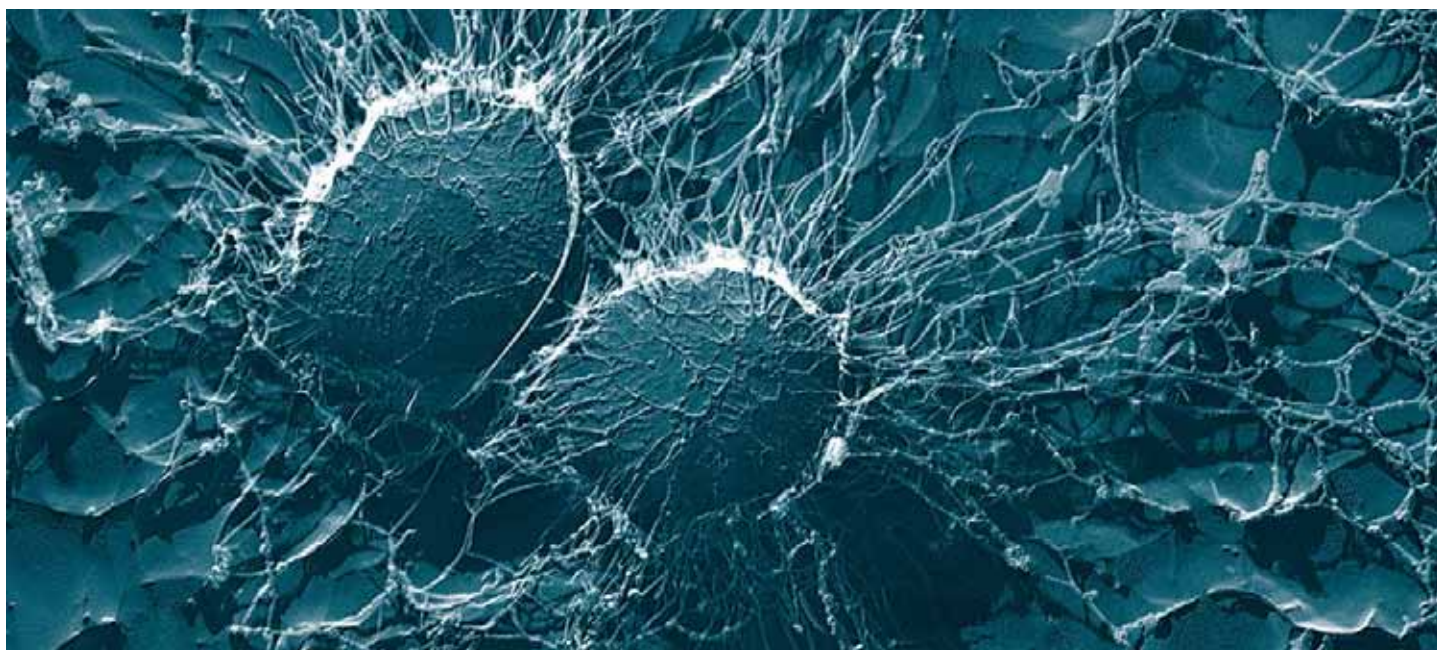
Plasmids facilitate the spread of antibiotic resistance genes, often acquired from environmental bacteria. This has been an important factor in antibacterial resistance in pathogens. Screening environmental organisms for resistance to new chemical entities may allow a prediction of future resistance mechanisms.

As well as understanding mechanisms of drug resistance, knowledge about resistance development can suggest strategies to overcome it. For instance, well-established therapies combine a β -lactam antibiotic with an inhibitor of the bacterial β -lactamase that degrades the antibiotic.

Antibiotic development therefore needs to consider not just activity on isolated targets but how such targets will be accessed and possible mechanisms of resistance that could emerge.

One step forward may be to establish and prioritise the key research questions relevant to antibiotic discovery, research and development. These could be used by funding agencies to develop priorities or by researchers to orient their research in ways that will feed into practical antibiotic development but without necessitating a complete switch to translational drug development.

Staphylococcus aureus (Eric Erbe and Chris Pooley, USDA).



Leads: Natural, synthetic, or both?

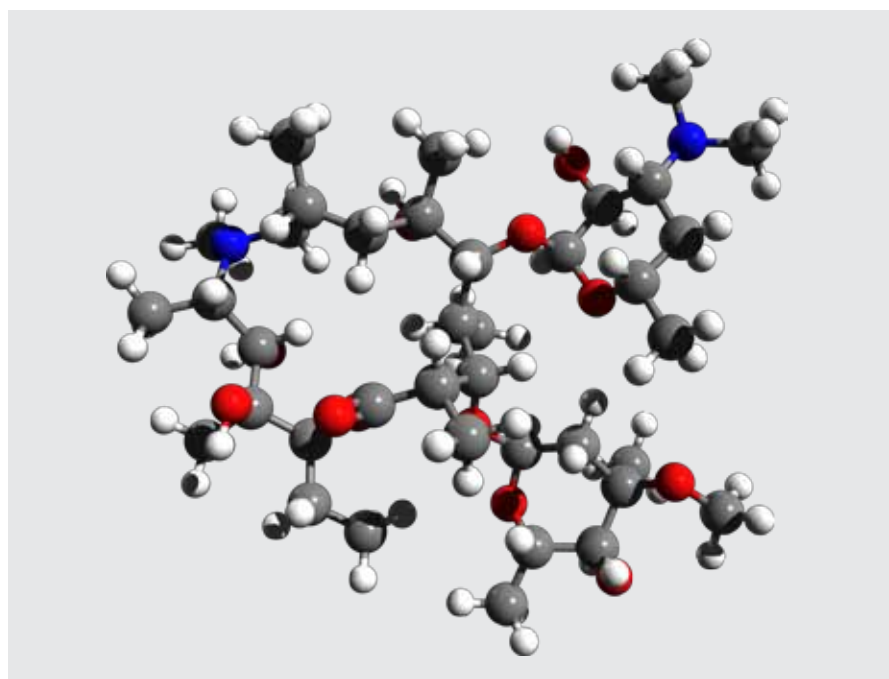
Early antibiotics were developed from natural products, most notably compounds produced by other bacteria or fungi. With the growth of combinatorial chemistry, the emphasis shifted to high-throughput screens of large chemical libraries. Over the past decade, industry-based work on natural products has almost disappeared (although there has been small growth in the biotech sector and a steady increase in activity in academia).

It is likely that all easily accessible natural products with antibiotic properties have already been exploited. Nonetheless, the natural world remains a large untapped source of new leads. These may come from plants or micro-organisms living in unusual environments, but even those closer to home could be harbouring useful compounds – the vast majority of environmental bacteria cannot be cultured in the laboratory so have not been screened for useful products. New culture techniques, a focus on slow-growing organisms or on microbes from marine or other unusual environments, or metagenomics-based approaches could be fruitful avenues to explore. Activation of 'cryptic' biochemical pathways may also reveal previously unknown metabolites with antibiotic potential.

In addition, new screening methods – especially whole-cell screening technologies, which also generate information about targets – will be a more productive way to generate leads. Since target access is critical, whole-cell screening is preferable to biochemical approaches as it also assays the ability of compounds to gain entry to cells. With methods for rapid determination of structure, a compound showing minimal inhibitory activity but able to access an intracellular target could be used as a starting point, with later chemical modification to enhance efficacy.

With industry retreating from antibiotic development, chemical libraries have been divested to biotech companies, contract research organisations, not-for-profit bodies or academia. Although they are a potential source of new leads, it is not yet clear how useful such resources are likely to be.

Azithromycin (Giorgiopl2).

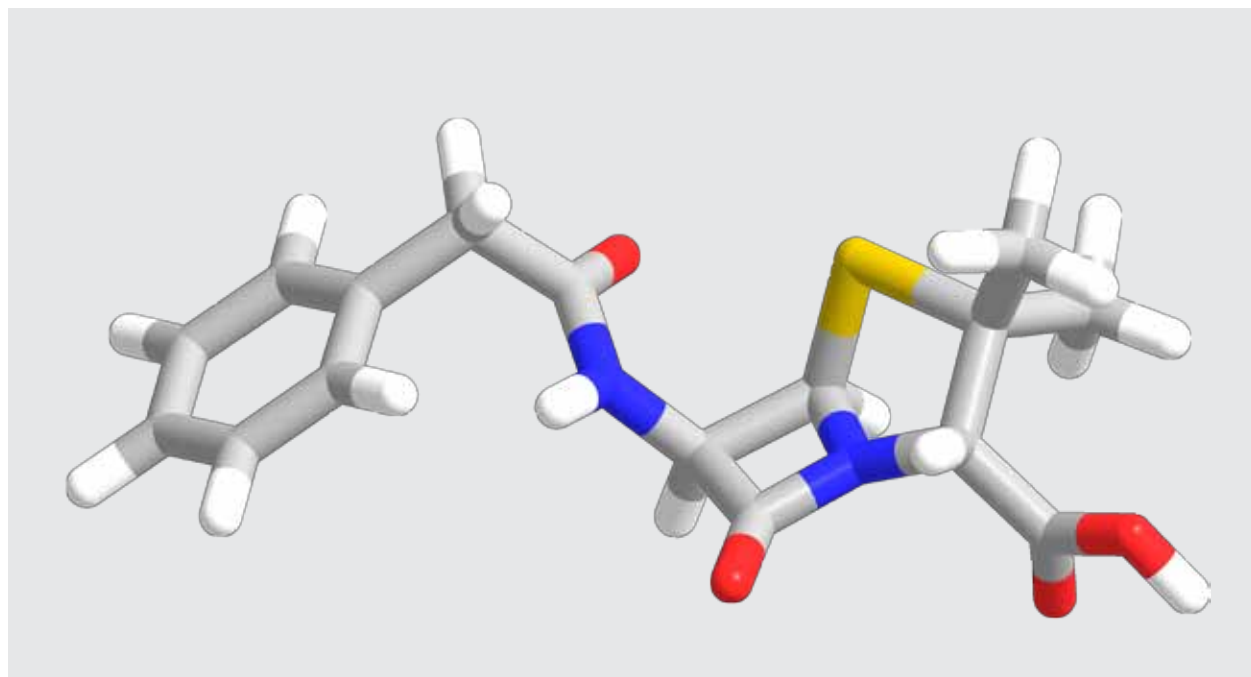


The innovation landscape: Infrastructure and skills

The retreat of industry has had a profound impact on the innovation landscape. To a degree, commercial antibiotic discovery, research and development has been taken up by the biotech sector. But there has undoubtedly been a significant loss of skills in antibiotic development in industry, with a 'skills gap' developing as few new researchers have entered the field, which is now dominated by a small group of commercial laboratories. It is essential that scientific expertise in antibiotic development is not lost completely, and that a new workforce – both in academia and in industry – is developed with equivalent skills.

One approach may be training courses for academic researchers interested in antibiotic R&D. Skills development could be further enhanced by greater interactions between industry, the biotech sector and academia. Recent years have seen a greater emphasis on pre-competitive cross-sector research collaborations and 'open innovation', with more research activity and information sharing in the public domain and commercialisation starting later along the translational pathway. However, such initiatives require detailed discussion about how intellectual property is managed.

Penicillin G (Cacyle).



Funding

Although there is some funding available in the USA and EU for basic bacteriology research, and also some schemes to encourage collaboration between industry and academia, there is only one explicit scheme for tackling antibacterial resistance and the lack of new drugs. The 'NewDrugs4BadBugs' programme, part of the EU's Innovative Medicines Initiative (IMI), a joint undertaking between the EU and the European pharmaceutical industry association (EFPIA), is committing some €429.7m (half from the EU and half from industry) to joint projects between industry, academics and clinicians to tackle the lack of new antibacterial drugs.

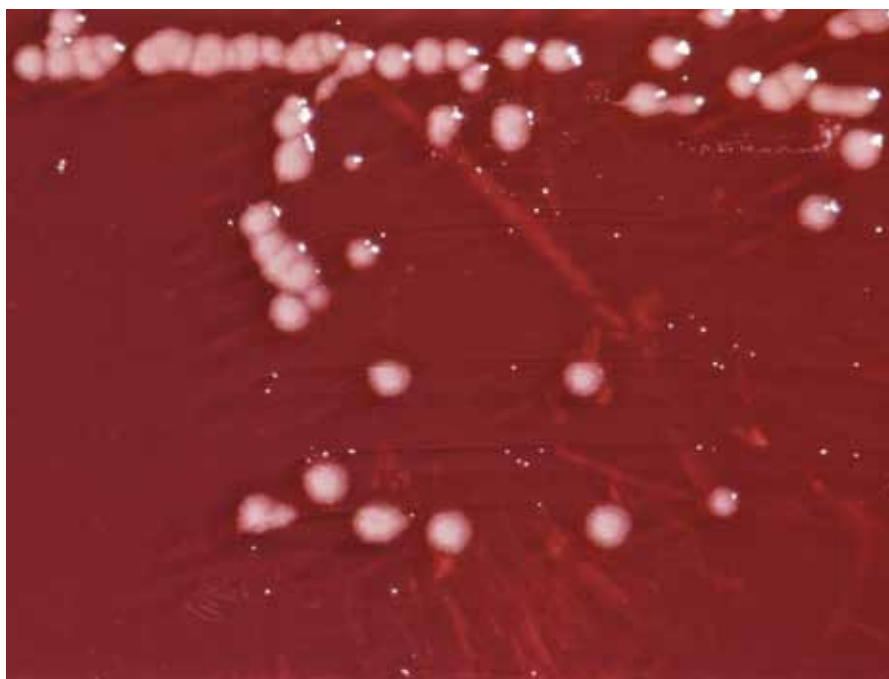
In the USA, the Department of Health and Human Services' Biomedical Advanced Research and Development Authority has committed US\$67m to Tetrphase and potentially up to US\$200m to support the development of a portfolio of antibiotics by GlaxoSmithKline.

However, many new entities to treat bacterial infections are likely to be required – between five and 20 new drugs within the next 20 years. Taking into account the recognised attrition rate of drug development (including antibiotics), this implies that several hundred discovery, research and development programmes are required.

An additional possibility is the funding of community resources or tools. Although typically falling outside the schemes supporting hypothesis-driven research, such resources can often be funded through other mechanisms when communities can collectively make a strong case for an initiative that would benefit an entire field.

Although collective action may be beneficial, the exact nature of collaboration is open to debate. Large consortia may be one approach, providing the benefits of coordination but potentially at the risk of stifling innovation and loss of flexibility. Looser collaborations may be more productive but less focused on specific endpoints.

Pseudomonas aeruginosa (CDC).



Conclusions

Given the alarming rise in antibiotic resistance and inadequate drug pipeline, how can academic researchers respond to the urgent need for new antibiotics?

Researchers often maintain that their work offers hope of new therapies. However, it is insufficient to assume that an essential gene product is a viable target for antibacterial drug discovery, research and development. To turn this aspiration into a reality, researchers need to take a rigorous approach to target identification and validation. The pharmaceutical industry mantra 'fail early, fail cheap' can apply to academic antibiotic discovery, research and development – identifying early that a target or therapeutic lead is flawed and abandoning development means that valuable funds and time can be devoted to projects more likely to succeed.

Irrespective of the source, funding for this area should be competitive and open to all including academia and the biotech sector. Awards must be based upon quality as judged by experts in antibacterial discovery, research and development.

Some research groups may wish to exploit their discoveries and move to translational studies. The research process is different, however, and the shift may not be suitable for everyone. More fundamental research is still required for antibiotic development, however, by tackling issues such as uptake and efflux and mechanisms of drug resistance. It may be helpful to establish a prioritised list of research questions to guide such work.

Progress may also be quicker if academic, biotech and industry establish mechanisms to collaborate within a precompetitive space, such as public–private partnerships. There is a role for national funding agencies in this process, as long as proper due diligence is performed. Collaborative structures may also benefit skills exchange, though other schemes for professional development and training courses may also be needed. In particular, it would be helpful to establish career pathways for researchers in antibiotic discovery, research and development, which make allowance for the high likelihood of failure in drug development.

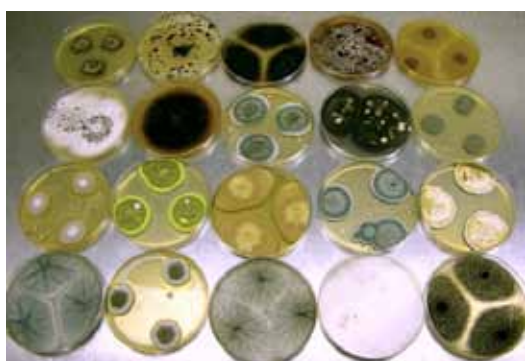
A potential analogy could be drawn with cancer drug development, where centres exist to carry out research on a portfolio of lead compounds, from target validation to clinical trials. This could be based on several centres of excellence or a single 'virtual national centre' – in essence a national consortium – and would provide a coherent framework for the development of new antibiotics, including a suitable skills base.

Such models still rely on the pharmaceutical industry to take on and develop products. Given that the conventional financial model for antibiotic discovery, research and development no longer works, radical alternatives may be needed to take account of market failure. One approach would be for the entire process to be undertaken within the public sector, with priorities driven by public health needs rather than profit. An alternative idea that has been mooted has been for the equivalent of a 'Marshall Plan' – with a large-scale commitment of public funds to be lent to enterprises driving forward the development of antibiotics.

Given both the scale and the urgency of the problem, it is essential that these issues are addressed as rapidly as possible. Academia, industry and funders need to identify ways to progress work to replenish the antibiotic pipeline, to minimise the very real risk of global catastrophe.

Top: Antibiotic resistance tests (Dr Graham Beards).

Below: Ascomycetes (Dr David Midgley
Cultures: Dr David Midgley University of
Sydney, Australia).





The 'Lessons to be Learnt' symposium was supported by:

