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New antimicrobial drugs: why we need them and how we can get them

A non-technical summary of a meeting organised by the European Academies' Science Advisory Council in Hannover in March 2014. It is based on EASAC's statement *Antimicrobial drug discovery*, which is available at www.easac.eu.

Introduction

'Antimicrobial resistance poses a catastrophic threat. If we don't act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that can't be treated by antibiotics. And routine operations like hip replacements or organ transplants could be deadly because of the risk of infection.'

Professor Dame Sally Davies, England's Chief Medical Officer, speaking about her 2013 Annual Report

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The annual reports of Britain's chief medical officers of health do not always make headlines. The one issued in 2013 certainly did—and gave new life to the discussion of a fear that was first expressed some 60 years ago by Alexander Fleming, the man who discovered penicillin. Recognising the capacity of bacteria to adapt to changed circumstances, he suggested that they would inevitably find ways of resisting the damage to them caused by antimicrobial drugs. So it has proved.

In spite of periodic attempts to tighten controls on the misuse or overuse of antimicrobial drugs in human and veterinary medicine and agriculture, the problem posed by microbes that have acquired the genetic information to make them resistant has grown steadily worse. To take one example, bacteria resistant to otherwise effective drugs kill 25,000 people annually in the European Union (EU) through sepsis, a condition in which the body's immune system goes into overdrive and sets off a series of reactions including widespread inflammation, swelling and blood clotting.

One remedy for this looming return to a pre-antibiotic era is, of course, to develop new antimicrobial drugs. Regrettably, the past

25 years have witnessed a stagnation in drug development in this field. It is this combination of a worsening problem and a fall in the number of new drugs coming to market that has created the present crisis.

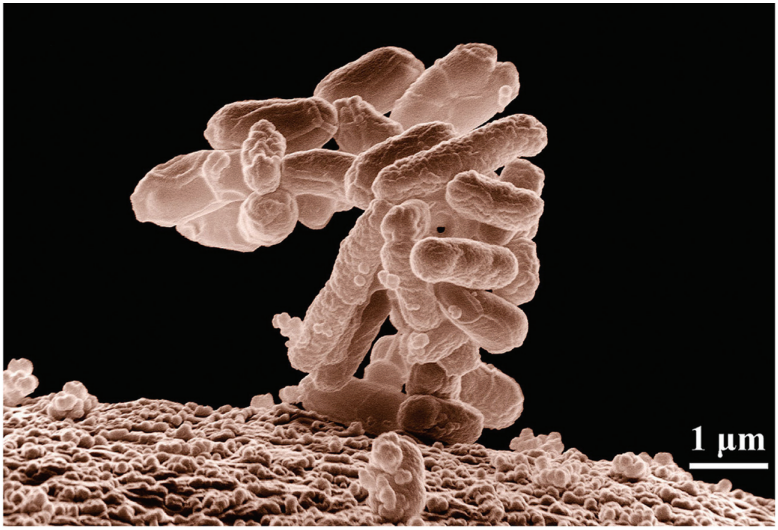
Professor Davies was one of a group of scientists from across Europe who were brought together by the European Academies' Science Advisory Council (EASAC) to consider what might be done. Although the outlook is still grave, the meeting did offer considerable grounds for optimism in that scientists who study drug resistance have come up with a great many ideas for tackling or preventing it.

That said, it will take political will, sound administrative organisation and appropriate funding to turn these ideas into clinical reality. Good science is the first step, but not the only one.

Where have we gone wrong?

In one sense we haven't. Evolution by natural selection is continually adjusting all living things to cope better with their environment. Microbes are no exception. Moreover they breed rapidly, go through many generations in a very short time, and are correspondingly quick to adapt. If their environment is made toxic by drugs, mutant varieties that can cope with the new conditions will eventually appear.

Microbes can defend themselves against drugs in many ways: by acquiring the skill of inactivating the drugs, for example; or by preventing the drugs penetrating their outer layer; or even by pumping drugs out once they have entered. Resistant microbes, having a selective advantage over their non-resistant counterparts, will



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Escherichia coli *bacteria: presenting increasing problems of antibiotic resistance.*

survive and replicate, increase in numbers, and spread their resistance through the population. In this sense the emergence of resistance at some level is almost inevitable.

Where we have gone wrong is in not trying hard enough to minimise the rate at which this occurs. The more that antibiotics are used, the more rapidly it will happen. Antibiotics should therefore be used only when necessary, and then at doses and for periods of time that ensure that all the microbes involved are eliminated. A too frequent use at too low a dose and for too short a time simply promotes resistance.

In the early days of antibiotics they were used without regard for the emergence of resistance. Some with a value to human medicine were fed routinely to farm animals as growth promoters. This, too, helped to create an environment in which resistance could appear. Now we know better—but a tendency to be careless in using them lingers on.

Once the simplest drug targets had been exploited, the cost of developing new antimicrobials that worked in new ways began to increase. For sound commercial reasons the pharmaceutical industry preferred to invest in other areas, especially in chronic disease where drugs might be taken for years or decades, not just a few weeks or even days. The number of antibiotics in the development pipeline began to fall.

How can we find new antibiotics?

The first antibiotic, penicillin, got its name from the *Penicillium* mould that naturally produces it. And naturally occurring products, many derived from fungi or other microorganisms, have always been a common starting point for the development of new antibiotics. The belief that we have now exhausted what Nature has to offer is not correct.

The fact that a product is natural does not necessarily make it suitable, unaltered, for human therapy. It may have unwanted side effects; it may not occur in a form that the human body can easily absorb or otherwise deal with. The natural product is frequently just a starting point for chemists who will try to modify its molecular structure to boost its desired actions and eliminate its unwanted ones.

Delegates at the Hannover meeting saw a need to improve on the methods of medicinal chemistry traditionally used to get the most out of natural products. Newer technologies are now available, but not yet fully exploited. Advances in genetics and biosynthesis can be used to create 'libraries' of molecules, some of which may have minor alterations that confer particular value if the molecule is to work as a drug.

Another approach relies on what it is called 'genome mining': in essence, looking for genes within an organism, such as a mould, that might code for new drugs, but which are not usually active when it is cultured under standard laboratory conditions. Change those conditions and the organism may start to produce a different set of possibly valuable products.

Still more ingenious …

Although the traditional view within the pharmaceutical industry has been that the only good pathogenic bacterium is a dead one, this is not necessarily so. Many microbes harm their hosts because they make what are called virulence factors. These are molecules that help them to undertake various essential tasks such attaching themselves to their hosts, evading or inhibiting that host's immune defences, and gaining entry to or exit from their host's cells. Efforts to develop drugs that in some way target and neutralise these factors may turn a pathogenic bacterium into a relatively harmless one, vulnerable to the host's own immune defences.

Another and even more ingenious use of novel target selection is applicable to microbes that rely for sustenance or viability on factors within the contents of the host's cells. In such cases it might be feasible to target a drug not against the microbe itself but against whatever in the host it relies on. The Hannover meeting heard about case studies in which the objective of therapy is to block, transiently at least, certain host cell functions that incidentally also support the invading microbe. A study of influenza A virus, for example, has identified certain host cell targets as essential to virus replication but not essential to the viability of the host's cells. Novel anti-influenza drugs that attack these targets are now being generated. Targeting a drug not at an invading microbe but at something in the host you are aiming to defend is paradoxical—but perfectly reasonable if the host can cope with the loss.

New life for older approaches

A prodrug is the term used to describe an agent that the patient's own body converts into an active drug. The history of antimicrobial research offers many familiar examples including prontosil and metronidazole. But prodrugs, for some reason, have slipped out of favour. Some experts think they merit a revival. The time is ripe to revisit existing libraries of prodrug candidates, and to look for new ones.

Some microbes are not easily cultured in the laboratory. A renewed exploration of this most fundamental of microbiological tasks might find new culture methods, and allow hitherto neglected microbes to be grown and studied in the hope of discovering previously unknown chemical products. Also warranted, is to consider repurposing old drugs: looking at therapeutic agents designed for one purpose in the hope of finding other and previously unrecognised uses.

As already pointed out, many antimicrobial drugs have been based on chemicals produced naturally by living things. Some people believe, erroneously, that as a source of new agents Nature is now exhausted. This is not so. The insect world, for example, has yet to be fully exploited. Insects are an evolutionarily successful group showing great diversity. It would be surprising indeed if their chemistry was not equally varied—and it is. The rat-tailed maggot of the drone fly, for example, produces enzymes that can degrade the material of biofilm, the gelatinous matrix secreted by many bacteria to confer a form of security, not least in helping them resist the onslaught of antimicrobial drugs. Another insect with potential is the harlequin ladybird, which produces a compound called harmonine with a broad spectrum of antimicrobial activity. There are other insects known to have potentially useful chemistry—and many more to be investigated.

Prof. Dr. Andreas Vilcinskas (Justus Liebig University Giessen; Fraunhofer Institute for Molecular Biology and Applied Ecology IME)

The harlequin ladybird: a potential source of new antimicrobial agents.

Recommendations

The Hannover meeting concluded that much needs to be done to enhance antibiotic innovation. Better drug targets need to be identified; more high-quality clinical research facilities need to be built; regulations need to be streamlined; and commercial hurdles need to be tackled so that companies are attracted back into this area of drug development.

To meet these broad objectives the delegates compiled a list of six broad recommendations.

1. Support for basic research

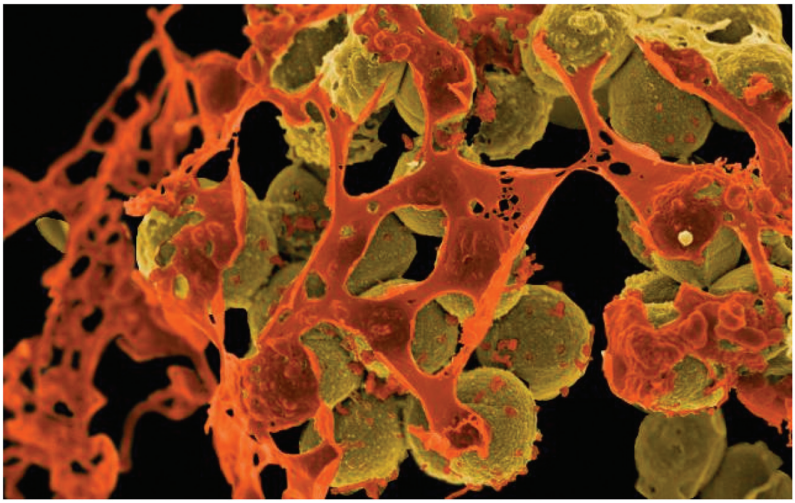
The European Commission and Member State funding agencies should support more basic research relevant to antimicrobial drug development. This should include the study of virulence factors, host–pathogen interactions, new mechanisms of action and the exploration of new and promising chemical structures.

Increasing investment in fundamental research would make the field more attractive to young investigators. It might also help to revive the training of scientists in the relatively neglected discipline of medicinal chemistry, and reverse the migration from the EU of skilled pharmaceutical company staff.

Problems of antibiotic resistance can be exacerbated by the actions of medical staff and their patients: the former by prescribing too liberally, the latter by demanding antibiotics when there is no justification for their use. Mindful of this, there is a need for more social science research to understand and then to find ways of influencing such behaviour.

2. Support for new compound identification and development

New scientific opportunities are becoming available. These include the exploitation of new natural product sources such microbes found in extreme environments,



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Methicillin-resistant Staphylococcus aureus *bacteria.*

the culture of hitherto unculturable organisms, the greater use of prodrugs, and the development of new delivery systems. We need to understand the rules that govern the penetration of drugs into cells.

3. Addressing the bottlenecks in preclinical and early clinical development

There is currently a problem in the EU caused by a lack of the expertise and resources that allow academics to test interesting agents in animal models, move them swiftly to proof-of-principle stage and so attract the attention of industry. The US National Institutes of Health have recently announced a new initiative called 'Accelerating Drug Discovery' to tackle the disconnect between the early identification of biological targets and the production of effective treatments. It brings together government, non-profit and industry stakeholders—and might serve as a model for antibiotic innovation in the EU.

It is essential to increase the public funding for preclinical activities in the EU. Resources might be structured in various ways. A single, centralised EU institution is one option; but a more distributed model, such as a virtual institute, could work as well. Equally urgent is the need to consider new funding sources for these preclinical development activities—the European Investment Bank, for example. In some cases it will also be desirable to seek new funding for subsequent early clinical development. A not-for-profit consortium could be set up to draw income from Member States, international organisations and pharmaceutical companies.

Clinical research depends not only on funding but also on the availability of skilled clinical researchers. The EU should create opportunities to sustain skill development in infectious disease research, and to facilitate faster recruitment of patients into trials. International collaboration, particularly with the US National Institutes of Health,

would minimise pointless duplication of research, and make the most of limited or expensive infrastructure such as handling facilities for disease-causing micro-organisms.

4. Optimising EU partnerships

Current scientific partnerships between academia and the pharmaceutical industry, as exemplified by the Innovative Medicines Initiative (IMI), are welcome. To improve the performance of the IMI it is essential that pharmaceutical company partners are encouraged to contribute their best assets (compounds and ideas) to pre-competitive joint projects, and that the IMI has the flexibility to explore new findings that emerge during these projects.

The Joint Programme Initiative on Antimicrobial Resistance, which allows EU Member States to agree research needs and so avoid duplication, is also welcome. However, it is underfunded for the development of new drug leads, and the funds it does have are spread too thinly.

5. Rethinking regulatory frameworks

Some current regulatory frameworks are hindering the search for new antimicrobials; the various regulatory authorities should agree on, for example, requirements for the registration of new drugs. For those with a narrow spectrum of action, for combinations of established therapies, or where the need is critical, regulatory requirements could be simplified.

There should also be a renewed commitment to conditional licensing under which early marketing of drugs for which there is only limited clinical trial data is supported by comprehensive monitoring of those drugs during routine use. Some flexibility in regulatory frameworks is essential if health care systems are to prepare themselves to face unexpected or emerging threats.

6. Raising public awareness

These scientific, technical, regulatory and economic challenges cannot be tackled without increasing their public visibility. Better public engagement is needed to explain the global threats and new pressures; to educate people about preserving the efficacy of antibiotics currently available; to encourage support for research and innovation, which necessitates the use of animal research; and to understand that the expectation of new therapies with zero side effects is unrealistic.

Conclusion

Action on resistance to antimicrobial drugs is needed at all levels: local, regional and global. EASAC's member academies have an important and continuing responsibility to raise public awareness and political interest in tackling the pressing need for new medicines. Without such awareness and interest the likelihood of success in facing up to the threat posed by microbial drug resistance will be significantly, perhaps dangerously, reduced.

Unless we take concerted action on microbial drug resistance, the problem will simply get worse.

EASAC – the European Academies' Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in providing advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard. EASAC was founded in 2001 at the Royal Swedish Academy of Sciences.

Through EASAC, the academies work together to provide independent, expert, evidence-based advice about the scientific aspects of public policy to those who make or influence policy within the European institutions. Drawing on the memberships and networks of the academies, EASAC accesses the best of European science in carrying out its work. Its views are vigorously independent of commercial or political bias, and it is open and transparent in its processes. EASAC aims to deliver advice that is comprehensible, relevant and timely.

The EASAC Council has 29 individual members and is supported by a professional secretariat based at the Leopoldina, the German National Academy of Sciences, in Halle (Saale), and by a Brussels Office at the Royal Academies for Science and the Arts of Belgium.

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