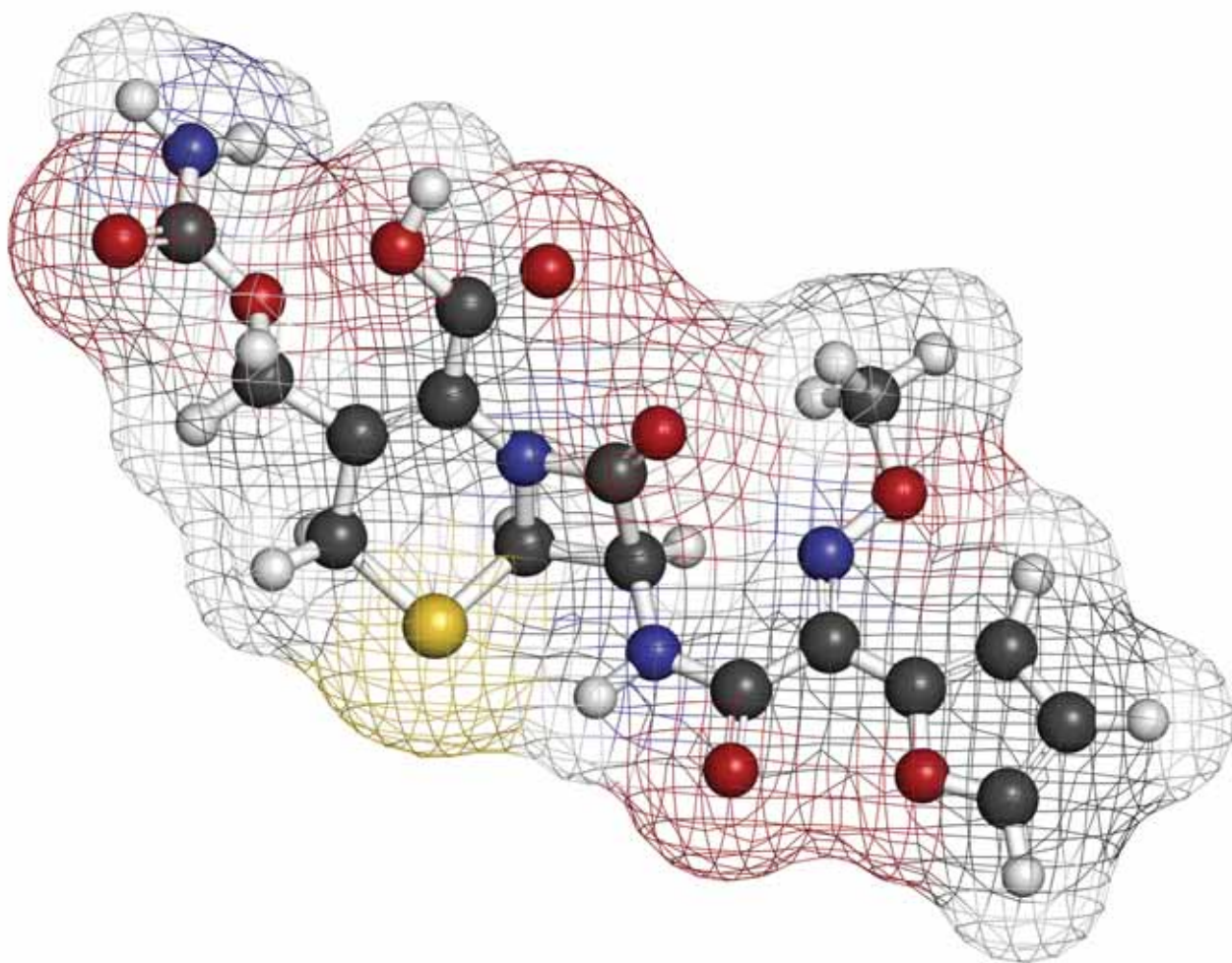


Antibiotic resistance: a deadly future

New ideas to fight a global health crisis

Sally Davies / Dilip Nathwani / Nicholas Brown / Debbie Porter



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BY THE NUMBERS

Antimicrobial resistance: a quantifiable problem

Antimicrobial resistance is already thought to contribute towards **25,000** deaths within the EU per year

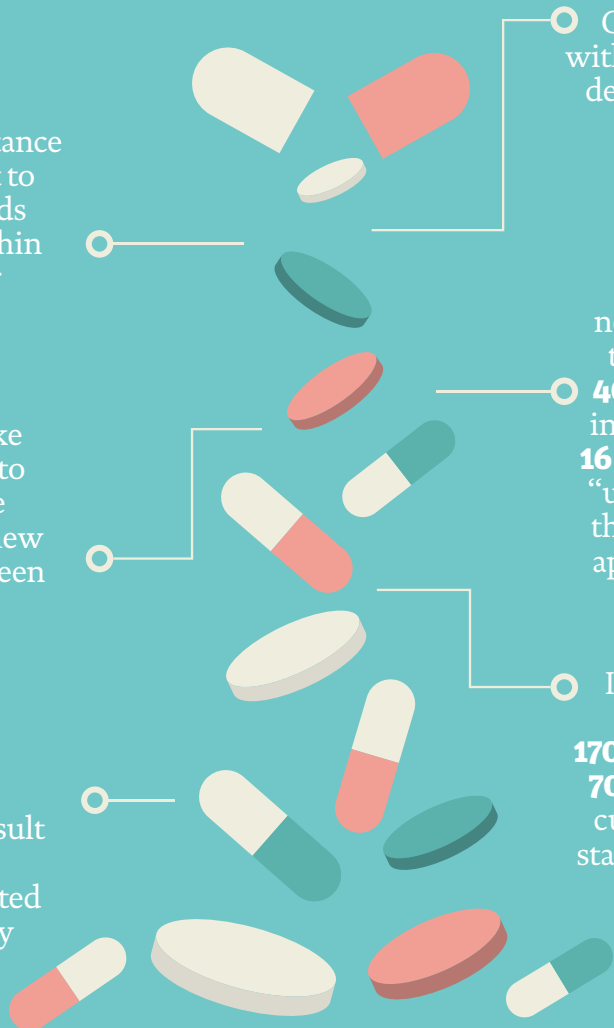
Medicines can take around a **decade** to develop, and the development of a new drug can cost between **\$1.2-\$2.6bn**

The loss to EU healthcare and productivity as a result of antimicrobial resistance is estimated at **€1.5bn** annually

Of the 36 companies with antibiotics in clinical development, just **five** fall in the top 50 pharmaceutical companies

New antibiotics are needed, but at this time there are only around **40** potential candidates in clinical development. **16** of these are considered “urgent”, but only **six** of those are expected to be approved between 2017 and 2024

In contrast to new antibiotics, over **170** diabetes drugs and **700** cancer drugs are currently in various stages of development



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Recognising a global health crisis

Debbie Porter, executive director of speciality care at MSD, explains what industry is doing to mitigate the effects of antimicrobial resistance, and what governments can do to support these efforts



The past two decades have seen growing evidence of the societal threat of antimicrobial resistance (AMR). More recently, public sentiment has shifted from recognising AMR as a reality rather than a threat. Currently, AMR is predicted to overtake cancer as one of the leading causes of mortality worldwide, resulting in up to 10 million people dying each year by 2050, and costing \$100 trillion globally. AMR is an inevitable consequence of antibiotics and halting its advance is impossible due to the nature of evolution. Nevertheless, slowing the progress and impact of AMR can be achieved with effective antimicrobial stewardship, surveillance, infection control, education and vaccination. Just as important is ensuring innovation delivers a continuous flow of new treatments for deployment when new, resistant organisms emerge.

A collective push for change

Historically, the major source of antibiotic innovation and production has been the pharmaceutical industry. However diminishing returns have led several large companies to discontinue investment in antibiotic research. This is in part because, despite antibiotics underpinning a wide range of procedures, the perceived societal value has been low.

In September 2017, the World Health Organization (WHO) published a report on the global antimicrobial development pipeline, stating that the number of new innovations coming through was insufficient to mitigate the risk of AMR.

Additionally forums such as the UN, G7 and G20 have debated the issue, considering interventions to boost research and introduce payment reforms to reflect the value of antibiotics and encourage investment.

As a result, there has been notable progress on “push” incentives, such as

early stage research grants and public-private partnerships, but considerably less progress on “pull” incentives, which seek to better reward developers of an antibiotic upon regulatory approval or throughout its time on the market

Achieving pull through

At the 2016 World Economic Forum, a group of pharmaceutical companies committed to exploring solutions that reduce the link between company revenues and volume of antibiotics sold. A new model with this aim could help imbue market certainty, offer protection to healthcare payers and possibly increase access to antimicrobials where there is a genuine need.

It is unlikely, however, that a one-size-fits-all solution to funding will work. Instead, broad concepts of reform need to be agreed upon internationally, for the purposes of tailoring specific solutions at the national level.

The UK, already a leader in the AMR policy debate, could be one of the first to start to redefine its purchasing and supply arrangements. Recognition of the antibiotic market failure within the Life Sciences Industrial Strategy is a crucial step, but sustained political support is required for change to be realised.

Brexit looms large, bringing with it great uncertainty, but the threat of AMR will persist regardless of negotiations in Brussels. The potential for a positive leadership story, should the NHS decide to pilot a new model, is within reach.

Collaboration vs. coordination

The temptation to watch and wait for the actions of neighbouring countries is strong, but the geographic variance and speed at which resistance to antibiotics can emerge means the situation demands far more collaboration between countries than global coordination. Governments should view this as an opportunity to innovate individually, sharing learnings to assess if such reforms do, collectively, achieve the desired “pull” effect.

Success should be self-evident, with fewer patients faced with fighting a potentially deadly, “untreatable” infection.

A cut to your finger could soon be life-threatening



Professor Dame Sally Davies, chief medical officer, explains the scale of antimicrobial resistance, and what needs to be done now to prevent future disaster

Picture a world where bumping your elbow or grazing your knee could be cause for serious concern, where simple infections are untreatable and millions die from ailments we now easily treat. This is the post-antibiotic world we face if we don't act now to curb the rise of drug-resistant infections.

Already resistant strains of infections such as TB, HIV, malaria, and other common bacterial infections are estimated to kill more than 700,000 people annually – this is expected to rise to 10 million per year by 2050 if we do nothing. Earlier this year in the US a woman died after contracting an infection that none of the 26 antibiotics available in the country could cure. This is a scary glimpse of the reality that we must try to avoid.

I remember first stepping onto a ward as a young clinician and being in absolute awe of the power of antibiotics – I still am. These drugs have been and still are the bedrock of modern medicine.

Before antibiotics and vaccines, around 40 per cent of all deaths were due to infections; it's now just 7 per cent.

They are often our last line of

defence against some nasty ailments, but as many will know the effectiveness of the drugs we have in our armoury is in decline. Our inappropriate use of these precious medicines has led to infections becoming resistant and it is getting worse.

The problem is exacerbated by a lack of new drugs coming through. Worryingly, we haven't had a new class of antibiotics developed since the 1980s.

It is also a problem we have been warned about for decades. Sir Alexander Fleming even foreshadowed this phenomenon when accepting his Nobel Prize for discovering Penicillin, the first antibiotic, in 1945.

So why haven't we fixed the problem? The answer is, predictably, complicated. The very nature of drug resistance is that infectious diseases continue to mutate which alters the effectiveness of the drugs we use to treat them and every country faces unique challenges.

In the UK we are making good progress but we must do more.

Firstly, we must reduce the number of infections occurring in the first place. The UK government has therefore put in place an ambitious target to reduce a set of healthcare



associated infections by 50 per cent by 2020/21. This is challenging but better hygiene and infection prevention is essential.

Next, we need to build on our progress and reduce antibiotic use across the human and animal sectors even further. That is why the government committed to halving the inappropriate use of antibiotics in humans by 2020/21 and reducing animal antibiotic use to 50mg/kg by 2018. That animal use target has recently been achieved two years early, a huge testament to the commitment of those involved but this is just the first step. We will soon set sector specific targets to be achieved by 2020.

In the UK, we have some of the best clinicians and researchers in the world; we must help clinicians and make better use of diagnostic tests so they know when it is appropriate to prescribe antibiotics.

The UK will continue to invest in new research and encourage incentives for pharmaceutical companies to develop new classes of antibiotics and alternative options such as vaccines. We know developing these is slow, costly, and do not have a high success rate or good financial return. We must redress this.

This is not an issue just for the white jackets to fix; the public must play a role too. We have come a long way in educating the public on antibiotics with campaigns like antibiotics guardians. We need to go further; for the first time ever, Public Health England is rolling out a national awareness campaign so more people understand the importance of preserving the effectiveness of antibiotics and using them appropriately.

The UK is a world leader in its response and has been generating international momentum. There are serious international issues which need to be addressed. Surveillance across the world is inconsistent; there are glaring gaps where we simply do not know how many drugs are being prescribed and used, or what bugs are of particular concern. If we do not address this problem many countries will not only undermine international progress but

will also be at risk of failing to meet the United Nations Sustainable Development Goals (SDGs), which are hugely important. As such the UK government is investing £265m in the Fleming Fund to develop surveillance capacity in developing countries.

It is only through engaging civil society, governments, industry, and the third sector worldwide that we can tackle this.

The first step, achieved last year, was to put this firmly on the global political agenda. We secured a ground-breaking UN Declaration from all 194 Member States last September. But real action has been far too slow to follow and we're not where we should be.

That is why the UK government last month hosted landmark "Call to Action" with the Wellcome Trust, Thai and Ghanaian governments, and the UN Foundation to bring together key players and collect tangible commitments.

This conference brought together government leaders, industry experts, philanthropists and civil society to accelerate actions that will get real results, and make sure we target our efforts where they are most needed.

Developing a full global picture was one of our key announcements from that conference. The UK government is working with the Bill and Melinda Gates Foundation, Wellcome Trust, Institute for Health Metrics and Evaluation and University of Oxford to collect data on drug resistant infections globally and to map the impact. This will be critical in targeting our efforts appropriately.

This is a world-first. Since 2014 the UK government has invested more than £615m in research at home and abroad to get this done – £162m of which has been assigned in the past year and the UK is committed to continuing its efforts.

It is essential that other government, industry, professional and civil society leaders across the world do their bit.

Only a coordinated response spanning continents will underpin our efforts to stay ahead of drug-resistant superbugs. We must do this work now, or suffer the consequences.



No new class of antibiotics has appeared since the 80s

Antimicrobial resistance: the challenge of our lifetime

Professor Dilip Nathwani and Dr Nicholas Brown of BSAC explain how different bodies can mobilise against a drugs crisis

Opportunity beckons

Antimicrobial resistance (AMR) sits alongside climate change and terrorism as one of the three greatest threats on the global risk register, such is the magnitude of the danger it poses to human health. AMR reduces the effectiveness of antibiotics, and without them there can be no treatments for the common or complicated infections related to cancer, cystic fibrosis, heart transplants or joint replacement surgery, to name a few.

The good news is that the issue of AMR is firmly in the global spotlight with a rush of political activity in recent years. The World Health Organization (WHO) is leading nations in strategies to contain and reverse the risk AMR poses. In 2016, the UN General Assembly issued a declaration on AMR – only the third time health

has featured on the UN agenda in 71 years. The UK has played a leading role with the then Prime Minister David Cameron establishing the AMR Review under the leadership of Lord Jim O’Neill. In addition, learned societies, scientists, industry, and the wider healthcare community have been working together to meet the challenges of AMR through many initiatives aimed at regulation, education, funding, and clinical practice.

The not-so-good news is that despite concerted efforts, policy is not translating easily into practice. AMR hits the purse of shareholders because the return from the sale of antibiotics is undermined by reduced shelf life, and because new antibiotics are held back for “last-line” therapies when other antibiotics have failed. New

financial incentives, innovative funding models for antibiotic research and public-private and industry-academia partnerships to drive the development of new and effective treatments are urgently needed. While funding to support innovation in new drug discovery is welcomed the support for innovation in educational solutions has lagged behind. The healthcare sector also needs funding and support for a range of innovative learning solutions such as comprehensive open access training and education to ensure they prescribe effectively.

One cannot help wondering if these shortcomings might be linked to a lack of tangible outcomes by which to measure the success of national action plans and strategies – and by the lack of consistency between strategies in terms of terminology, areas of compliance, and recommendations. Who can say, for example, whether the EU and UK regional action plans are successfully aligning with those of the WHO? What would success look like in a developing country, where access to antibiotics for the wider population is perceived as a greater problem? And how can we demonstrate what difference the politicising of AMR is achieving?

Policy into practice

Despite the inevitable difficulties, there are moves to translate policy into practice through emerging initiatives like the Conscience of Antimicrobial Resistance Action (CARA) and WHO’s AMR Community of Practice. CARA, an independent alliance, seeks to support and monitor implementation of the UN declaration on AMR. Although still in its infancy, CARA is already working with partners across human and animal health under

the One Health Agenda, looking at how progress on the UN draft declaration can be measured.

The WHO expert group on healthcare professional workforce education and training is looking at how to create a community of practice to house AMR knowledge and toolkits. Offering a channel for dialogue, the community would enable practitioners, no matter what their economic landscape, to contribute to and freely access a range of tried and tested resources that can be adapted for local use. Such a community of practice will offer opportunities for those in Europe and the northern hemisphere to support low and middle-income countries (LMICs), and in turn for LMICs to offer valuable lessons in how to achieve much with little. It is imperative that such recommendations are translated into action with speed, without excess bureaucracy.

This network could be supported by organisations like the Centre for Infectious Disease Research and Policy (CIDRAP), which provides advice and analysis on the prevention and treatment of targeted infectious diseases, antimicrobial stewardship and public health preparedness. Bodies like CIDRAP and CARA can help to ensure we all deliver on the promises made. For example, BSAC and CIDRAP have identified a specific need around information and a diverse range of educational resources for antimicrobial stewardship that has global value through an approach that allows local adaptation. When the UN returns to the subject of AMR in 2018 and beyond, health professionals, journalists, and campaigners, should be able to check progress against the UN declaration by using indicators both WHO and CARA are developing.

While new coalitions, initiatives, actions and funds are crucial, it is equally important that we do not neglect existing priorities – most notably, equitable and universal access to old antibiotics. WHO has provided a promising start here by updating the antibiotics section of its Essential Medicines List for the first time in the list's 40-year history. But, suffice to say, more must be done, and soon.

Building capacity

One sector with the capacity to support further action is made up of professional medical charities and societies from around the globe. This sector's activities are trained on local, national, regional, and global collaboration. Free from the structures that often slow down governmental and federal bodies, many of these organisations can work collaboratively to deliver high-impact, low-cost initiatives at the point of need.

By way of example, the British Society for Antimicrobial Chemotherapy is a 900-member strong organisation of 40 years standing. British by name, the organisation has global reach and influence with representative members in 33 countries. The society has an active portfolio that covers research, surveillance, education and collaborative activities. It was responsible, in collaboration with the University of Dundee, for developing the innovative Massive Open Online Course on Antimicrobial Stewardship. Hosted by FutureLearn, a leader in open access online education, this free six-week interactive multi-media course was developed in less than 15 months. It ably demonstrates a timely response to need and underlies the power of digital learning as a means of educating a diverse global

community. Launched in October 2015, more than 45,000 learners from 42 countries have accessed the course already. The net cost has been less than \$4 per user to date. It is a development model that governmental bodies may wish to adopt and spread, and which philanthropic, and other, funders might look to support. The course has been translated into Mandarin, and with support from the British High Commission Science and Innovation Fund, the course will be launched in Spanish and Russian in 2018, with a bespoke shorter course planned for Africa. Translation of such courses with the inclusion of case studies relevant to the geographical and healthcare context ensures local ownership and engagement.

Civil society organisations such as BSAC are rigorous in their approach, basing their work on evidence and professional consensus, which allows them to function as honest brokers between policymakers, practitioners, industry, and the public. While their purses are not limitless, their ability to harness world-leading expertise and insight often is not. Imagine the opportunities that could be met if civil society was resourced in the same way as governmental bodies.

AMR really is the health challenge of our lifetime, and there needs to be a significant operational shift in the way capacity is identified, built and used. The answer is at our fingertips, it now needs to be matched by a political will to work openly and collaboratively. Imagine if governments could harness the connected resources of all learned societies working in the AMR arena. The gap between policy and practice would soon close. This is one opportunity that must be harnessed, and harnessed soon.

MSD is implementing a holistic approach to combating infectious disease



For over 80 years, MSD has been engaged in the fight against infectious disease, including the production of penicillin to help soldiers during World War II.

Our role in tackling antimicrobial resistance.

Today, MSD is one of only a few large pharmaceutical companies that has sustained a focus in research and development to treat infections caused by antibiotic-resistant pathogens and to develop vaccines to prevent infectious disease in both humans and animals.

A holistic approach.

We support calls to tackle antimicrobial resistance holistically - accounting for prevention and treatment of ill health in both humans and animals. United by a common goal, we have committed our resources and engaged policy-makers the world over to help find sustainable solutions to what is undeniably one of the greatest societal challenges of our age.

We are proud of our legacy and the fight continues. Together we can make the crucial difference.

For more information, visit www.msd-uk.com



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