

Antibiotic resistance: stemming the tide

Innovation in the face of a global health crisis



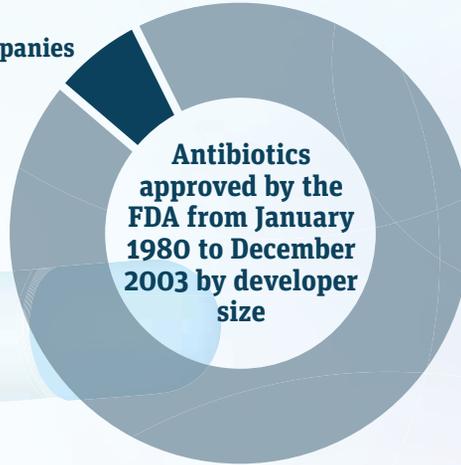
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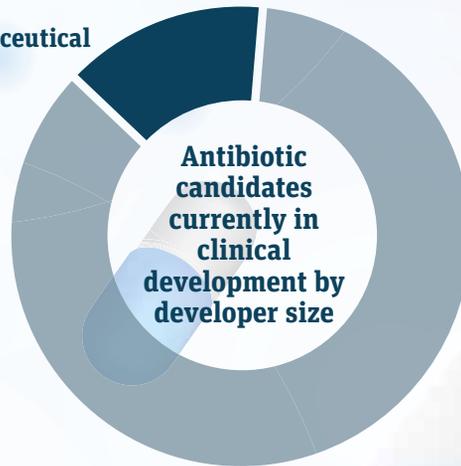
The changing antibiotic development ecosystem: Innovation has shifted from large to small companies

7%
small companies



93%
large pharmaceutical companies

15%
large pharmaceutical companies



85%
small companies



Data from Spelberg et al (2004) "Trends in Antimicrobial Drug Development", Clinical Infectious Diseases and the WHO-funded 2018 pipeline review published in The Lancet Infectious Diseases

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Daring to break the mould: can the UK be first?

Debbie Porter,
executive director,
speciality care at
MSD reflects on
progress made
in antimicrobial
resistance, and
what more needs
to be done



The world is losing the battle against antimicrobial resistance (AMR). Projections indicate that without serious intervention, the problem could end up costing ten million lives globally each year by 2050, more than are currently lost to cancer. The cost to the world economy could be \$100tn.

Last year, the WHO reported that the global pharmaceutical pipeline was still “insufficient to mitigate the threat of antimicrobial resistance”. This means there are not enough new antibiotics in development to keep pace with the rate at which today’s antibiotics are rendered ineffective by continuously evolving bacteria.

Many important advances in modern medicine, including surgical developments and chemotherapy, could soon become too dangerous to use if doctors can’t rely on antibiotics to protect patients against infection while they are vulnerable.

World Antibiotic Awareness Week (12-18 November) is a chance to reflect on how to address this growing threat, and attract investment back to this crucial field of medicine.

In recent decades a number of large, research-based pharmaceutical companies have left the antibiotic market. One reason for this is that healthcare systems across the world seem to undervalue antibiotics relative to other medicines. The use of new innovations can be delayed by the fact that hospitals often hold

them in reserve until all others have been exhausted (resistance has developed). This creates an uncertain market for companies seeking to recoup the cost of drug development.

Those of us that remain in the antibiotic market still invest significantly. In 2016, members of the AMR Industry Alliance invested more than \$2bn in AMR-associated research and development. But the long-term trend of large companies leaving the market looks set to continue; a further two left this year.

That’s why MSD, with industry colleagues, has been working with the Department of Health and Social Care to design a reimbursement model that breaks the link between a company’s revenue and the total volume of antibiotics sold to the NHS – a concept known as “de-linkage”. It’s comparable to insurance. Companies would be paid a fixed annual sum to make available as much or as little of an antibiotic as is required. This would protect the NHS budget from unexpected rises in demand (such as an outbreak of a resistant infection) while offering manufacturers predictable revenue. Crucially, this model promises improvements in both the availability and appropriate use of antibiotics in the hospital setting.

Companies have now submitted products for a pilot scheme, and the prospect of achieving a world first seems attainable. But implementation needs to be accelerated if we are to begin reversing the trend of companies leaving this space. UK action alone won’t achieve this, but to create a ripple effect of global reform and stem the tide of AMR, someone must go first. As the UK looks to bolster its leadership in a time of Brexit, there are few better examples of low-hanging fruit with which policymakers could help solidify the nation’s commitment to life sciences at this crucial time.

Chair of the APPG on Antibiotics Julian Sturdy argues it is time to stop and reflect on the state of antibiotics, and chart a vital policy course to avoid future casualties

With AMR, the stakes could not be higher



In this year of significant anniversaries, ranging from the centenary of the Armistice to the National Health Service's seventieth birthday, one particular milestone passed with barely any recognition. Friday 28 September marked ninety years since Sir Alexander Fleming discovered penicillin and medical science entered the antibiotic age.

The tale of Sir Alexander returning to his disorderly laboratory and accidentally making one of the greatest medical discoveries in history is well-known, less widely known is that the Nobel Prize winner was also acutely aware of the drawback of antibiotic resistance from the very beginning.

Ninety years on, increasing

resistance to antibiotics poses the very real threat of plunging us into a medical dark age where routine surgeries, caesarean sections and some cancer treatments risk becoming life-threatening as antibiotics become redundant. This is what lies ahead if we do not successfully address the challenge of drug resistance; the stakes simply could not be higher.

The O'Neill report attributed 700,000 deaths across the globe to anti-microbial resistance in 2016. "Attributed" is the crucial word here as the formal cause of death is the infection the deceased was resistant to, rather than their inability to fight the disease. Alarming, it is expected that this will rise to ten million deaths per year in 2050 without sufficient action. To put



this into perspective, this figure is higher than the current number of people who die from all types of cancer in a given year.

As chair of the All-Party Parliamentary Group (APPG) on Antibiotics I have met with groups and individuals who are leading the efforts to face down this global threat, and their expertise and commitment give me hope that it is possible to prevent catastrophe. However, this can only be done if all of us play our part. The APPG exists to raise the profile of antibiotic resistance, the need to preserve antibiotics through education on their appropriate use, the lack of new treatments for bacterial treatments, and to help accelerate efforts to discover, research and develop new drugs. Our scope shows quite

clearly that the solution to antibiotic resistance is not to be found solely in the laboratory.

Last year the British Society for Antimicrobial Chemotherapy published a report on behalf of our APPG that assessed the UK's progress on recommendations made by the World Health Organisation back in 2011. Interestingly, the report found that the UK Action Plan had struggled to address both the area of education and public awareness, and incentives for antibiotic discovery, research and development.

Today, one in five antibiotic prescriptions issued in Britain is unnecessary. This underlines why it is essential we make progress on developing point-of-care diagnostic tools to identify the cause of infections when patients visit their GP. When a diagnosis is unclear it is possible for antibiotics to be prescribed for viral infections.

I would like to see firm leadership from the government to address the sizeable number of prescriptions that are unnecessary. Achieving this measurable objective will require more than improved diagnostics, and it is clear we need a better approach to raising public awareness of the risks associated with antibiotic misuse. Doctors can only prescribe, it is down to individuals to ensure they take the full course of antibiotics regardless of when they feel better.

The other area where Britain has not made sufficient progress is in relation to supporting efforts to discover, research and develop new drugs. As with most products, the profitability of drugs and new treatments is linked with sales. However, in the case of antibiotics we want to restrict their use and only use new antimicrobial classes as drugs of last resort. This means that the traditional reimbursement model offers no incentive to

pharmaceutical companies to invest in the research and development of new antibiotics.

Much focus has been given to the "push and pull incentives" for antibiotic development and it is clear we need a new business model that will ensure product development is viable even if the drugs sit on shelves mostly unused for decades. Should the UK government simply fund new research and purchase large stocks of antibiotics? I think this will be an important element of the eventual solution, but unilateral action will always be difficult given the free-rider problem in an international context. Therefore, I would like to see moves towards a global fund.

The Health and Social Care Select Committee has expressed concerns that the treat of antimicrobial resistance has fallen off the government's agenda and called for "more visible and active leadership". This is something that the APPG on Antibiotics has requested for some time, but the truth is that we need greater support in Parliament to communicate this message.

Therefore, to mark World Antibiotics Awareness Week, running this year from 12 to 18 November, I am hosting a parliamentary drop-in event for MPs and Peers to learn more about this global challenge with the hope they will then agree to join a parliamentary caucus. Ministers should be encouraged by this development because it is very much a two-way street. We are calling on them to ensure antibiotic resistance remains high on the government's agenda, and in return we shall play our part in raising public awareness and promoting the cause through Parliament.

The solution will not be found in a discarded petri dish – every one of us needs to step up to the mark.

The broken antibiotics development market demands action



Tim Jinks, Wellcome's head of drug-resistant infections programme, argues that the development of life-saving drugs is under threat from the lack of action by government and industry

Drug-resistant infections kill 700,000 people a year. That could rise to an estimated ten million a year by 2050, if we do not act now. A key part of the response is developing new antibiotics, so we have effective options in reserve as established treatments fail. These new antibiotics need to be made accessible to those who need them and used appropriately, to avoid unnecessary increases in resistant infections. A combination of aligned investments will be needed to achieve this.

Smaller companies are already playing their part. Organisations such as Achaogen, Bugworks, and Melinta Therapeutics have become major innovators. In fact, over 80 per cent of antibiotics in clinical development today are being studied by small companies. These companies don't have deep pockets or diverse drug portfolios. But fuelled by outside investment, often including public funding from organisations and schemes such as CARB-X, they are intent on bringing new antibiotic

breakthroughs to markets.

And yet funding typically runs out after early clinical trials. At that point, companies face a struggle to raise further private investment or attract a buyer to complete a drug's development and get new medicines to patients. If they do clear that hurdle, they face the further costs of regulatory approval, manufacture and distribution.

In the past, large pharmaceutical companies would step in at this point to take new antibiotics to market, and generics manufacturers would extend their reach across the world. But we can no longer rely on this happening, and the delivery of new antibiotic medicines is perilously close to failure.

Antibiotics simply aren't an attractive investment opportunity compared to other therapies. Recently-launched cancer drugs are expected to return a net profit of up to \$8.2bn per drug to their developers; new antibiotics struggle to break even. They compete with cheap, generic antibiotics, and their



use is often limited as part of stewardship measures to prevent unnecessary increases in resistant infections. In 1980, there were 25 large pharmaceutical companies with active antibiotic discovery programmes. Today, following recent exits by AstraZeneca, Sanofi, Allergan and Novartis, there are four.

Such exits are not easily reversed. Drug candidates are out-licensed; expertise dissipates, as researchers retire or change fields; data and trials results are lost; development and manufacturing facilities are

repurposed; and money is invested elsewhere. Without this vital part of the development ecosystem, breakthroughs will die on the vine for lack of a route to market. If the trend of disinvestment continues, new antibiotics will not be developed at the rate required by public health.

It is not only our ability to treat infections that will suffer. Surgeries and immune-suppressing treatments such as chemotherapy, which rely on effective antibiotics to mitigate the risk of infection, will be compromised. In the long term, large pharmaceutical companies will damage their own interests, as the utility of their other products is reduced.

No-one expects industry to make a long-term commitment to loss-making activity. New incentive models that reward investment and get products to patients are needed. There are plenty of ideas, such as lump sums for the successful development of drugs that meet certain needs, or paying for the right to access a product rather than pill-by-pill. Work has started on delivering such models, in the US and the UK. But governments must act with greater urgency and resource, and pharmaceutical companies must engage constructively in these efforts.

As part of this, companies should recognise that antibiotics may never again be blockbuster drugs. The scale of public investment warranted in this area means that private rewards should not be excessive, and there should be an appropriate balance of risk between the private and public sectors. Access to and the stewardship of antibiotics that meet the most urgent public health priorities must be prioritised.

A range of interventions and reforms will be needed to deliver innovative medicines and make them accessible, but the role of large pharmaceutical companies is crucial. They have the manufacturing

capabilities, global networks, and supply and distribution chains to deliver at the necessary scale. GSK, for example, sells over 28,000kg of antibiotics each year. Yet its drug Augmentin – the best-selling branded antibiotic in the world – is registered in only 71 countries.

This is currently the best-case scenario. The Access to Medicines Foundation has found that antibiotics introduced to the market in the last 6 years have, on average, been filed for registration in fewer than five of 106 low and middle-income countries considered. The lack of access to antibiotics in these countries still results in more deaths than resistant infections, and that lack of treatment options contributes to inappropriate antibiotic use and increasing frequency of resistance. The private sector needs to do more to make antibiotics accessible to the people who need them.

Small private companies now dominate research and development in this space, fuelled by growing public funding for early-stage research. But promising breakthroughs risk falling off a cliff as they reach late-stage development, which is increasingly abandoned by the large companies that have the scale and expertise to bring new antibiotics to global markets. We know that companies can't do expensive research for nothing, and that the commercial prospects for antibiotics are challenging. But those companies still weighing up their engagement in antibiotics development should really consider the long-term implications to their sector of short-term, narrowly commercial decision-making. Meanwhile, governments and companies need to redouble their efforts to address the market failure and create a sustainable system for bringing new antibiotics to market and to the people who need them.

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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