Antimicrobial resistance: calculating the cost

A Westminster Health Forum policy conference recently highlighted the economic impact of antimicrobial resistance. High on the agenda was the question: how can we incentivise the development of new antimicrobials? **Louise Frampton** reports.

Without effective antibiotics, over three million surgical operations and cancer treatments a year could become life threatening. In addition, experts predict that, in just over 30 years, antibiotic resistance will kill more people worldwide than cancer and diabetes combined.[1] Despite the global threat, the market has failed to incentivise the development of new antimicrobials. In the 1980s, there were 18 multinational companies committed to antibiotic research; today there are only a handful. It has been 30 years since a new class of antibiotics was last introduced, while only 3 of the 41 antibiotics in development have the potential to act against the majority of the most resistant bacteria.

Large pharmaceutical companies are continuing to abandon antibiotic research and yet resistant infections currently claim an estimated 25,000 lives across Europe, each year, caused by five resistant pathogens, including:

- *Escherichia coli* (*E. coli*)
- *Klebsiella pneumoniae (K.Pneumoniae)*
- *Enterococcus faecium*
- *Pseudomonas aeruginosa*
- *Methicillin-resistant Staphylococcus aureus* (MRSA)

According to Government figures, this adds over £1 billion to hospital treatment and societal costs.[2]

"AMR is not just a public health problem but an economic problem," warned Professor Brian Ferguson, chief economist at Public Health England. He cited the findings of the O'Neill review, which projected that 300 million people are expected to die prematurely because of drug resistance over the next 35 years (2015-2050). The review calculated that the world's GDP will be 2% to 3.5% lower than it otherwise would be in 2050, which means that the world can expect to lose between "60 and 100 trillion USD worth of economic output" if antimicrobial drug resistance is not tackled.

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"This equates to about 600 times the annual budget of the NHS," commented Prof. Ferguson. "This is a massive potential economic impact." He highlighted the need for incentives to encourage the development of new antibiotics, while pointing out that there are unique challenges when it comes to the development, management and use of antibiotics.

"The interesting problem, from an economic point of view, is that we are trying to design incentives for the production of a good that we want people to avoid using for as long as possible…Decoupling profits from sales volumes is terribly important. There is a consensus that we need a mixture of public and private action and investment across the value chain," Prof. Ferguson continued.

Dr. Julie Robotham, who leads on modelling and economics, for HCAI and AMR, at Public Health England, offered an overview of the current picture for antimicrobial resistance, highlighting the latest figures from the English Surveillance Programme for Antimicrobial Utilisation and Resistance.

"In terms of bloodstream infections, we've seen a 21% increase over the four years from 2014 through to 2018. Of these, we have seen a 32% increase in the number of resistant bloodstream infections. This is equivalent to around 60,000 resistant severe infections over the year in 2018. This obviously poses a burden for healthcare services and for the patients themselves, as these resistant infections may have greater morbidity and mortality associated with them," she commented. ▶

In view of this, reducing the risk of antimicrobial resistance is one of the top 10 key priority areas outlined in PHE's five-year strategy, through to 2025.

"We play a key role and are tasked with elements of the UK's *Five-year AMR National Action Plan*, so we contribute to the achievement of the ambitions around human health. The first of those is to reduce the incidence of specific drug resistant infections by 10% by 2025 and halving the number of healthcare-associated gram-negative bloodstream infections," Dr. Robotham commented.

She added that the second ambition is to "reduce antimicrobial use in humans across the UK by 15% by 2024". This ambition has included the goal of achieving a 25% reduction in antibiotic use in the community from 2013 and a 10% reduction in the use of 'reserve/watch' antibiotics in hospitals from 2017.

"To do this, PHE is working in very close partnership with the Department of Health and Social Care, NHS England and Improvement, and the devolved administrations. Integral to this is reducing health inequalities and this is a key component of all of this work," Dr. Robotham explained.

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Inappropriate prescribing is an issue.

PHE's Second Generation Surveillance System

Surveillance is an important component of Public Health England's work – this captures routine laboratory surveillance data on isolates and antimicrobial resistance from laboratories across England. Around 98% of NHS laboratories report to this 'second generation' surveillance system, with the majority reporting daily through automated systems.

This microbiological data can then be linked with clinical data, including antimicrobial prescribing, patient administration and hospital episode statistics, hospital admission data, and patient outcome and mortality data.

Dr. Robotham reported that a Unified Infection Dataset is currently under development: "This will link all of these things together, so we can obtain data on the whole patient pathway – through primary care into secondary care. We can obtain knowledge on when infections occurred along the pathway, where antibiotics were prescribed, and the resistance profiles of those infections.

"This will offer PHE and other researchers a huge opportunity in terms of what can be investigated, using individual patient level data. Potentially, we can predict resistance trajectories into the future and whether a patient's prescribing history impacts their risk of getting a (resistant) infection. We can look at risk groups in the population and also monitor the potential unintended consequences of driving down antibiotic use," said Dr. Robotham.

As well as disseminating data outputs to the ESPAUR Report, PHE also contributes to the Government's 'UK One Health Report', which looks at antibiotic use and resistance in animals and people, and the 'European Centre for Disease Prevention and Control Surveillance Scheme'.

Other schemes include 'Fingertips', which presents data on a number of indicators such as antimicrobial resistance, stewardship, infection prevention and control, and healthcare-associated infections. This enables CCGs to benchmark their performance across a range of indicators.

PHE has also developed a number of tools, education and training, both for the public and for healthcare professionals, to support campaigns – such as the 'Antibiotic Guardian' and 'Keep Antibiotics Working'. These aim to raise awareness and promote behavioural change both for patients and prescribers.

Antibiotic Guardian Campaign:

To become an Antibiotic Guardian, people choose one pledge on how they can personally prevent infections and make better use of antibiotics. To date, over 82,000 pledges have been made. (https://antibioticguardian.com) The Antibiotic Guardian website offers a range of resources – including posters, leaflets and videos, aimed at raising awareness of healthcare professionals and the general public. There are also patient stories that provide an emotive tool to convey the impact of antibiotic resistance.

Keep Antibiotics Working Campaign:

Research shows that inappropriate prescribing is, in part, due to patients expecting or demanding antibiotics, without understanding that they may not be effective for their illness. The focus of this campaign is on tackling this lack of understanding and thereby reducing patient pressure for antibiotics. The campaigns key aims are to:

- Alert and inform the public to the issue of antimicrobial resistance in a way that they understand and increase recognition of personal risk of inappropriate usage.
- Reduce public expectation for antibiotics by increasing understanding among patients about why they might not be given antibiotics, so reducing demand.
- Support healthcare professional change by boosting support for alternatives prescription

TARGET toolkit:

Also available is the 'TARGET' toolkit, which aims to influence prescribers' and patients' personal attitudes, social norms and perceived barriers to optimal antibiotic prescribing. It includes a range of resources

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that can be used to support prescribers' and patients' responsible antibiotic use. TARGET stands for:

- Treat
- Antibiotics
- Responsibly
- Guidance
- Education
- Tools.

While antibiotic prescribing is decreasing in general practice, there has been a small increase, in recent years, in hospital prescribing.

"We now need to evaluate what the reductions in prescribing will actually mean in terms of resistance across the population and in the longer term. We also need to be able to improve the evaluation of interventions in terms of their effectiveness and cost effectiveness, including stewardship and rapid diagnostics.

"The difficulty with this is that antibiotics are relatively cheap and potentially these interventions are more costly; the danger is that interventions won't be implemented in the short-term because they are deemed too expensive or too costly," commented Dr. Robotham.

To address this, she called for a change in current thinking: "If we prevent prescribing now, we are actually preventing the development of resistance and the potential harms of resistance in the future. We need to think about alternative methodologies to incorporate those potential future harms into cost effectiveness evaluations of interventions that are happening now," Dr. Robotham asserted.

There is significant research underway in this area. One such initiative is the 'STEP-UP' project, funded by the Economic and Social Research Council (ESRC) and developed in collaboration with the Health Economics Research Centre at the University of Oxford.

STEP-UP is a programme designed to improve the uptake and sustainability of effective interventions to promote prudent antibiotic use in primary care. The researchers are looking at different methodologies to the current cost effectiveness evaluation process, in order to capture long-term antimicrobial resistance costs and consider them within cost effectiveness evaluations.

While conserving antibiotics through effective stewardship and infection prevention will be crucial in the fight against resistance, Dr. Robotham also highlighted the need to stimulate new antimicrobial development. One policy that has been proposed in the UK is an insurance-based delinked model, where a one-off or series of 'insurance' payments is made to reward innovation and to delink revenue from volume of antimicrobials sold.

Dr. Robotham highlighted the latest research aimed at developing a 'Framework for Value Assessment of New Antimicrobials', conducted by the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) – a collaboration between researchers from two institutions (the Centre for Health Economics, University of York and the School of Health and Related Studies, University of Sheffield). (http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf)

The aims of the EEPRU research project are:

- To develop a framework that captures the expected value of a new antimicrobial;
- Consistent with this framework, to assess the implications of an insurance-based approach to reimbursement for the evidence and evaluation methods used as part of the National Institute for Health and Care Excellence (NICE) technology appraisal programme;
- To illustrate the framework using one or more case studies to highlight methods and evidence issues and alternative ways of addressing these;
- To suggest any changes that might be required to the methods used in the NICE technology appraisal programme;
- To make recommendations on each of these topics and identify any remaining issues and areas for further research.

Stimulating antibiotic development

Professor Hilary Thomas, chief medical adviser, KPMG, looked at established and proposed strategies for pricing and reimbursement of a novel class of antibiotic.

- **D-linked (insurance):** Proposed by several organisations including the US FDA and UK NIHR, this establishes a recurring ▶

fee for a set quantity of antibiotic for a fixed period, de-linking quantity from fee. The quantity bought is likely to be based on anticipated patient profiles and predicted AMR in the area. This reduces revenue uncertainty for the manufacturer, traditionally associated with novel antibiotics. However, the antibiotic will likely be held in reserve and used as a "last resort" therapy.

- **Premium price:** This is an established pricing model for selected new antibiotics. For example, Dificid (Merck) is priced at ~$3,500 *versus* $1,500 for vancomycin or $10 for metronidazole. This may be a 'high' reward for the manufacturer, depending on the level of use, and reinforces the limited use of a drug, which may be desirable. However, it draws negative perceptions from policy makers, patient associations and the public.
- **Option market for antibiotics:** This proposed model allows payers to buy the right, in the early stages of development, to purchase antibiotics at a discounted price should approval be granted at a later date. This distributes the financial risk across the developer and the payer. It incentivises the payer and developer through risk-sharing. However, the downside is that may limit the returns for the manufacturer. The initial models are aimed at antibiotics in early stages of development.
- **Market entry rewards:** This proposed model will provide a lump sum (~$1-1.5bn) to manufacturers. The value may be based on unmet need and efficacy data, and the fee may be paid within three years of launch. The model may provide funding for R&D as well as early launch activities. However, it is unlikely to cover the true cost of antibiotic R&D. Currently, no specific funding body has been identified. It may be paid through governments or international consortia.

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Antimicrobial resistance research and innovation

Dr. Jessica Boname, head of programme, antimicrobial resistance, Medical Research Council, UK Research and Innovation, provided an insight into current investment in antimicrobial resistance research and innovation.

The Medical Research Council (MRC) is one of the research councils that forms part of a new entity: UK Research and Innovation, which works in partnership with universities, research organisations, businesses, charities, and Government to stimulate research and innovation for future impact.

The MRC is working towards the UK National Action Plan on antimicrobial resistance, based on the framework for action developed by the Interagency Coordination Group on Antimicrobial Resistance. There are three main areas of focus:

- Reducing the need for antibiotics and unintentional exposure to antibiotics, which that takes into account the 'One Health' context (encompassing the use of antibiotics in animals and humans, as well as antibiotics in the environment).
- Optimising the use of antimicrobials in therapies – not minimising but optimising that use.
- Investing in innovation, supply and access.

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"We are interested in how infection and disease impacts humans. We're cognisant of the fact that there are influences from many different sectors, such as the food industry – infection can be transmitted via food, for example, while there are also impacts from animals in terms of zoonoses. This was recently brought to the fore with the coronavirus transmission, as seen in China. It is also important to understand potential threats from the environment – including the impact of human excretion into the environment," commented Dr. Boname.

A team from the Universities of Warwick and Exeter and the Centre of Ecology and Hydrology, for example, have scrutinised 69 areas of the river Thames and discovered high levels of drug-resistant bacteria near wastewater treatment works, showing how easily resistance can spread. The University of Exeter is also studying UK coastal locations – a study has sought to establish whether surfers are more vulnerable to the bacteria that pollute seawater and whether these bacteria are resistant to antibiotics.

The researchers asked 300 people, half of whom regularly went surfing, to provide rectal swabs, and compared the samples from surfers and non-surfers. The study, published in January 2018, found that regular surfers and bodyboarders are three times more likely to carry antibiotic-resistant *Escherichia coli* (*E. coli)* bacteria in their gut than non-surfers. The *E. coli* bacteria were resistant to cefotaxime, a commonly used and clinically relevant antibiotic. The study also found that surfers are particularly susceptible to ingesting the bacteria because they swallow up to ten times more seawater than sea swimmers.[3]

Regular surfers were also found to carry four times more bacteria containing mobile antibiotic-resistant genes, which can be passed easily between bacteria. Recognising coastal waters as a pathway for antibiotic

resistance is a step towards understanding antimicrobial resistance transmission dynamics. By learning how the natural environment influences this process, the aim is to support future approaches to protect human health.

"We work primarily to try to prevent infection. It is not all about new antibiotics – it is also about transmission: how can we interrupt the pathway of transmission between humans, animals and the environment in order to prevent infection in the first place. Prevention is nine tenths of the cure," Dr. Boname continued.

"We are also focussed on how we can improve diagnostics – to detect infections, but also to help understand which antibiotics are useful to clinicians. We need to understand the sensitivity and, most importantly, the resistance – this will allow us to establish the burden of the problem and what might be coming up on the horizon.

"We also look to contain infections once they've happened, so the use of antibiotics, the development of antibiotics and, importantly, alternative therapies are very much on our radar."

She explained that technology development plays an important part. Urinary tract infections can lead to bloodstream infections, for example, and research – funded through the MRC and Innovate UK – is seeking to develop a solution. The project is currently developing resistant materials which reduce the ability of bacteria and pathogens to colonise catheters, thereby lowering of the risk of infection and lowering the need for antibiotics.

"Within the MRC we ask questions about the biology of viruses and bacteria – how do they work, what are the mechanisms behind their virulence, and how are they transmitted between different individuals? We work at a molecular scale and at an individual host scale – looking at the host genetics and how this might influence an individual's ability to fight an infection without the need for external antibiotics.

"We are also working at a population scale – who are being infected within the community, country or, indeed, globally. We work through partners in UK Research and Innovation with other research councils to make sure that we have an interdisciplinary approach to tackling this important global problem. Microbiologists are not going to solve the problem on their own; they have to work with engineers and social scientists to understand behaviours around prescribing practice, for example."

Antimicrobial resistance is not just a UK problem; it's a global problem and it has to be tackled on a global scale. Therefore, MRC works in cooperation with other countries through the Joint Programming Initiative on Antimicrobial Resistance to ensure a coordinated approach to funding research to avoid duplicating efforts in different countries.

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Investment in research into new antimicrobials is vital.

"An improved antibiotic pipeline is really important. But we need to ensure we are not all trying to develop the same new antibiotic. We also need to find novel, interesting sources of new antimicrobials – such as sea sponges. These could be a source of interesting new compounds for new antibiotics."

A team from the University of Bristol, for example, has identified a sea sponge living 2km below the Atlantic Ocean that has the potential to fight one of the most common superbugs found in hospitals, MRSA. The team are now investigating how it responds to the human body to see if it can be used as an effective treatment in future.[3]

The MRC has also funded other important projects that could help reduce the use of antibiotics. Globally, each year, around 20 million patients in intensive care need machines to help them breathe, and many of these patients are treated with antibiotics.

The Proteus Interdisciplinary Research Collaboration, led by researchers at the Universities of Edinburgh and Bath, and Heriot-Watt University, are developing a bedside imaging tool that can detect whether harmful inflammation is present in a patient's lungs in less than a minute.

The technology uses a chemical probe, originally developed with funding from the MRC, with fibre-optic tubes that are small enough to be threaded deep inside a patient's lungs. The probe targets white blood cells that help the body fight off infection and, if inflammatory cells are detected, the probe causes them to light up. Detecting and identifying inflammation in this simple and quick way could help reduce the use of unnecessary antibiotics and speed up recovery in the most seriously ill patients.[3]

A team at Bristol Dental School has also been inspired by the antibacterial properties of cicada and dragonfly wings and are seeking to replicate this action for surfaces in materials such as titanium and polymer with the aim of using them for common medical implants.[3]

This could have significant potential for the development of hip implants, for example. With a rapidly ageing population and nearly a quarter of a million hip replacements already taking place in the UK each year, stopping infection in its tracks in this way would reduce patient trauma and save the NHS millions of pounds.

Ultimately, investing in research and innovation will be crucial in the fight against antimicrobial resistance, going forward. The Westminster Health Forum policy conference highlighted some key economic strategies for incentivising investment in new antibiotics and novel therapies, while highlighting how infection prevention can protect our antibiotic armoury and save money for healthcare providers. Above all, speakers reminded delegates of the potential high cost to the world of failing to act on what constitutes a "catastrophic threat to mankind".[4] CSJ

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