Antimicrobial resistance threatens to undermine our healthcare system

The immediate global challenge to human health and our economic stability due to coronavirus acts as a stark reminder that infectious disease preparedness cannot be ignored.

By Dr Peter Jackson

While antimicrobial resistance (AMR) does not present the imminent 'tsunami' of a viral pandemic, the ever rising tide of drug-resistant bacterial infections is nevertheless a critical challenge that we can no longer afford to ignore.

Antibiotic resistance is increasing to extraordinary levels across the globe. New resistance mechanisms are constantly emerging, putting in jeopardy our ability to treat common infectious diseases. Infections such as pneumonia, tuberculosis, sepsis and gonorrhoea are becoming much more difficult, and sometimes impossible, to treat as the armoury of effective antibiotics becomes depleted.

Where antibiotics can be bought for human or animal use without a prescription, the emergence and spread of resistance is made worse. Similarly, in countries without standard treatment guidelines, antibiotics are often over-prescribed by health workers and veterinarians and over-used by the public.

Without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill. Without new, innovative treatment options, the basis of our current healthcare system will be undermined, and procedures such as cancer chemotherapy, hip replacements, bypass surgery and caesarean sections will become highly risky due to opportunistic drug-resistant infections.

At the end of 2020, the World Health Organisation (WHO) published its third annual review of the clinical antibacterial therapeutic pipeline. It did not make pretty reading for those of us engaged in the development of new AMR treatments.

The headline message was stark: that the clinical pipeline remains insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance.

Eight new antibacterial agents have been approved since July 1, 2017, but overall they have low innovation and limited clinical benefit over existing drugs.

The current clinical pipeline contains 50 antibiotics and combination products and 10 biological drugs, of which 32 are active against at least one of the WHO's priority pathogens. However, just six of these agents fulfill at least one of the innovation criteria, and only two of these are active against the WHO's critical-priority multi-drug resistant Gram-negative bacteria.

While more than 40% of the pipeline consists of additional β-lactam and β-lactamase inhibitor combinations, there is a major gap in activity against the latest generation of 'superbugs': metallo-β-lactamase producers.

Unfortunately, the report's findings were not surprising. Over recent years, there has been a concerted effort to raise awareness of the looming crisis that AMR represents, at international and national levels, but awareness of AMR has not yet cut through to the public, more so when our attention is dominated by coronavirus.

That is why I believe that one thing which can

change rapidly is raising the awareness of patients and their loved ones to the fact that they are actually suffering from a drug-resistant infection. Too often terms such as 'complications of surgery' or 'you need stronger antibiotics' are used, rather than explaining fully the implications of AMR on their condition. We need to push forward the patient stories that demonstrate the debilitating impact that resistance to antibiotics can have, and the success stories where innovative treatments save someone's life. It is once we make these stories real, and less abstract, that the public will demand that governments, industry and regulators take action.

While there are signs that early-stage innovation is starting to blossom, the number of research scientists currently in the field focused on developing new antibiotics is perilously low, and only a handful of the major global pharmaceutical companies are investing in innovation. Many have withdrawn over the past decade due to the uncertain market conditions and the 'commoditisation' of cheap, older generic products, meaning that investors and company shareholders cannot see a way to recoup the hundreds of millions of dollars required to develop a new product. This is a major barrier preventing the new drugs we need being made available to patients.

At the heart of the problem is this: we need significant investment in new drugs to treat patients with critical unmet needs, but we also want to minimise the use of these new antibiotics to prevent reoccurrence of resistance to the new therapies.

Current reimbursement mechanisms and valuation metrics used by payers around the world are linked to agreeing a price likened to volume of sales, so are unable to address this need to 'delink' reward for innovators for their essential work while only using lifesaving AMR drugs sparingly.

There are several recent examples that demonstrate this market failure. Achaogen, a San Francisco-based biopharmaceutical firm, spent hundreds of millions of dollars over 15 years in the development of Zemdri, what was hoped would be an effective drug to treat urinary tract infections caused by drug-resistant bacteria.

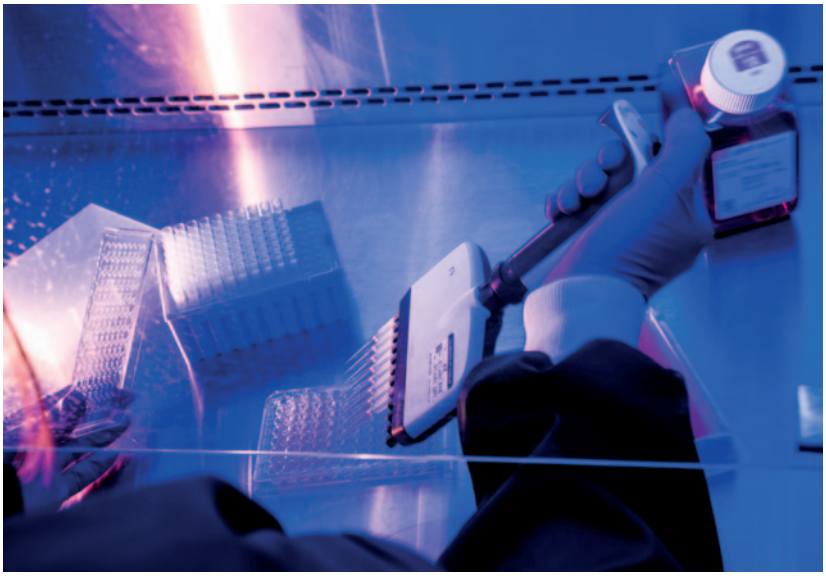
Zemdri was seen as an important option for treatment of carbapenem-resistant Enterobacteriaceae infections, among the most complex bacterial infections to treat. Achaogen also had numerous other antibiotics in its pipeline and it was therefore a hammer blow when in April 2019 the company declared bankruptcy. Despite making tangible progress and with a product in the works that was offering hope to many, Achaogen was unable to make a profit and its directors felt there was no other option but to bring proceedings to a halt in the face of mounting losses.

In a field where there are already so few companies developing new antibiotics, to see one of the seemingly more successful ones go under was devastating. An already bleak situation became worse at the start of this year when New Jersey's Melinta Therapeutics – another antibiotics firm – also filed for bankruptcy.

This all came off the events of 2018, when Novartis exited antibiotics, joining AstraZeneca, Sanofi, Bristol-Myers Squibb and Allergan in doing so. Upon announcing it was no longer pursuing antimicrobial research programmes, Sanofi also revealed that 140 jobs were to be lost in the process. Given the lack of potential other workplaces where the knowledge built up in the roles could be applied, it represented a detrimental brain-drain to the antibiotics sector, meaning we are globally less equipped to respond to new developments in AMR.

However, if we look to other parts of the world there is some cause for optimism. Small- or medium-sized enterprises (SMEs) are now the primary drivers of this sector. Although some of these businesses are struggling, primarily due to the costs of running clinical trials and difficulties identifying new targets, an infrastructure is developing that we hope will allow their ideas to flourish.

For example CARB-X, a global public-private partnership based in Boston, is providing significant support, in total up to $500 million, for translation of new projects from pre-clinical testing into clinical trials. Denmark's Novo Holdings has launched its Repair Impact Fund with the aim of investing $165 million in 20 AMR start-ups, early-



stage companies and corporate spinouts. Novo's director, Aleks Engel, has said that his confidence is boosted by the fact the proposals coming his way are much more innovative than the products that have recently failed.

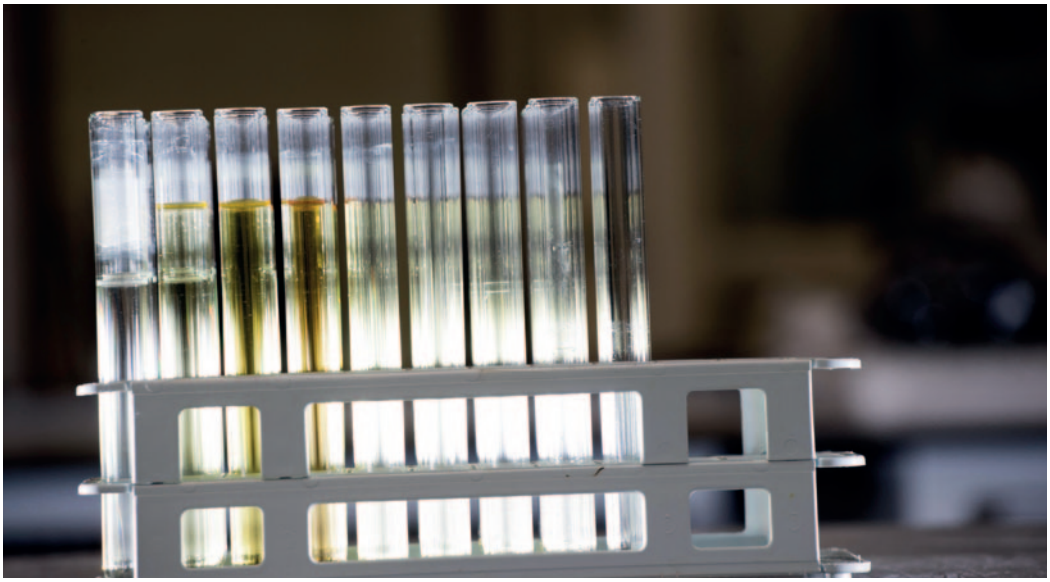
There are other areas that offer cause for optimism. The work being undertaken by the Global Antibiotic Research and Development Partnership (GARDP) initiative is bringing new treatment options for sexually-transmitted infections in both developed and less-developed regions of the world. GARDP works with partners to ensure sustainable access to treatments, promoting responsible use and affordability to all in need. It is aiming to deliver five new treatments for drug resistance infections by 2025, working with 50 public and private sector partners across 20 countries.

I believe there is still plenty of scope for further innovation in the AMR market, in particular with regards to encouraging a vibrant drug development ecosystem. The average new drug in other therapeutic areas passes through four or five owners on its journey from discovery to commercialisation – from universities and research institutes, through small and medium-sized biotech companies to global pharma majors. We need to encourage more transactions along the development pathway for new AMR drugs and it is essential that large pharma companies are an active and growing part at the apex of a healthy network. Big pharma needs to be an essential part of the AMR ecosystem, with its commercial, regulatory, supply-chain and stewardship expertise combined with global reach. That is not the case currently.

We also need to work harder at political engagement. At recent G20 meetings, there have been commitments made to help change systems to enable the development of new antimicrobial drugs, but, generally, these have not been met with action when the politicians return home. At times it seems that the complicated situation, with a timescale outside the electoral cycle combined with no real clamour from the public at large or effective patient advocacy, means that while the importance of the issue is recognised, there is a lack of progress in taking the actions required.

Thankfully the first signs of positive movement on reimbursement reform are appearing. In the UK, the National Health Service is collaborating with the National Institute for Health and Care Excellence (NICE) on a pilot project under which NHS England will evaluate and procure two AMR drugs on a trial basis – delinking the valuation and reward payments from the medicines' usage. It will test a 'subscription' style model that pays pharmaceutical companies upfront for access to drugs based on their usefulness and value to the NHS and wider society.

The project is part of the UK government's five-year, multi-agency action plan that includes improved stewardship to minimise the chances of resistant strains emerging. The plan is the latest step towards the government's broader 20-year vision, and includes the targets to halve health associated Gram-negative blood stream infections and further reduce antimicrobial use by 15% by 2024. The plan also supports increased use of a 'precision medicines' approach increasing the percentage of prescriptions informed by diagnostics and decision support tools.



This welcome move by the UK will make it more attractive for companies to invest in AMR R&D, and their shareholders to support them, sending a strong signal that the UK government is serious about fixing the broken market for the long term.

The NICE project is an important initiative but the UK only represents around 4% of the global pharmaceutical market. Sweden has recently announced its new approach, guaranteeing payments for companies that register their products in the Swedish market and maintain a supply chain.

The worldwide market failure will only be addressed if other countries act on market reforms, essential to bring big pharma back to the sector. The World Economic Forum (WEF) recently joined the chorus of industry voices calling for creation of such new 'pull' incentives such as market entry rewards. To date, we have mostly seen 'push' incentives such as research grants – directed mainly towards small and medium-sized biotech companies. These grants are not enough in themselves to tackle the core problem of major pharmaceutical companies withdrawing from R&D in this area.

The UK's AMR Centre (AMRC) is another important element within this emerging AMR ecosystem, providing an alternative pathway for drug developers to progress their projects into clinical trials, by offering in-kind pre-clinical and clinical development capacity in return for a share of future commercial revenues. July 2019 saw AMRC take forward an anti-virulence programme from the Japanese pharma company Shionogi. The project, COT-143, is a novel therapy designed to help the body tackle Pseudomonas aeruginosa (Pa) infections, a hard-to-treat and often drug-resistant pathogen recognised by the WHO as a critical priority threat to human health.

The pathogen is found in soil, water, skin and most man-made environments throughout the world. Because it thrives on moist surfaces, the bacterium is capable of contaminating medical equipment, including catheters, causing infections in hospitals and the community. It is associated with serious illnesses such as cystic fibrosis and causes severe infections including pneumonia and urinary tract infections. The consequences of such severe infections include drug-resistant pneumonia and sepsis, and often prove fatal.

COT-143 is a novel humanised monoclonal antibody. It does not kill bacteria directly but targets a virulence element that effectively disables the immune system from acting against the infection. COT-143 exerts its anti-virulence activity through inhibition of the PcrV component of the type 3 secretion system (T3SS), a key virulence mechanism of Pa. Pre-clinical studies and regulatory safety tests have delivered encouraging results and using our expert network across the north west of England, the AMR Centre is taking the programme forward to in-human clinical trials in NHS facilities during 2021, following manufacture of its complex active ingredient in 2020. If these clinical trials are successful, Shionogi aims to make this exciting new drug available to patients around the world, initially for patients suffering from persistent and recurring respiratory infections.

So while there are some emerging hopes for optimism, the past few years have been difficult for all of us in the field of AMR drug development, and there are credible reasons to suspect the next few years will be equally challenging. We have seen that the road to getting new AMR drugs to market is littered with stumbling blocks, but there is a growing awareness from governments, industry and regulators that things need to change. It will not be easy but the groundwork is currently being laid that will help fix the broken system and enable hugely important new drugs to get to market.

While the world's attention is rightly focused on the immediate threat from coronavirus, the key message is that effective infectious disease preparedness against AMR will save lives.

About the AMR Centre

Established in May 2016, The AMR Centre is a key part of the UK's response to the global threat from antimicrobial resistance. Based at Alderley Park in the UK, the AMR Centre is a company with public and private investors, to support/accelerate the development of new antibiotics through a fully integrated development capability, offering translational R&D through to clinical proof of concept. DDW

Dr Peter Jackson *is an experienced UK-based serial entrepreneur in the life sciences sector. Over the past 10 years he has created six new companies targeting novel therapeutics across infection, oncology and immunology, as well as in agrochemicals and life sciences services. Dr Jackson has more than 25 years' experience in the sector, previously holding senior executive roles as commercial director then VP of Avecia's Pharmaceutical Products business unit, following senior commercial and R&D positions at predecessor companies Zeneca and ICI. During 2015-16, Dr Jackson was chairman of the steering committee created to establish the UK's translational R&D centre focused on antimicrobial resistance, the AMR Centre, and now runs the enterprise as its executive director.*