Part of the conference series
Breakthrough science and technologies
Transforming our future

Advances in antimicrobial innovation

Held on 5 July 2021

Conference report
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Introduction

On 5 July 2021, the Royal Society and the Academy of Medical Sciences hosted an online international conference on Advances in antimicrobial innovation. This meeting, supported by AstraZeneca, forms part of the Royal Society's Transforming our Future series and the Academy of Medical Sciences' FORUM programme. These meetings are unique, high-level events that address the scientific and technical challenges of the next decade and bring together leading experts from the wider scientific community, including, academia, industry, government, and charities. The meetings are organised with the support of the Royal Society Science, Industry and Translation Committee.

The conference series is organised through the Royal Society's Science and Industry programme which demonstrates the Society's commitment to integrate science and industry across its activities, promote science and its value, build relationships and foster translation.

The Academy's FORUM programme brings together industry, academia, and the NHS, as well as the charity, regulatory and wider healthcare sectors. It provides an independent platform to bring together leaders from across the life sciences sector to discuss scientific opportunities, technology trends, translational challenges and strategic choices in healthcare

The programme was organised by Professor Jeff Errington FMedSci FRS (Newcastle University), Dr Flic Gabbay FMedSci (tranScrip Partners) and Dr David Powell (Summit Therapeutics). The conference commenced with a talk on research priorities, advances in innovation and lessons from COVID-19, leading onto a talk on the future of reimbursement for antimicrobials. The conference then saw talks on novel research and approaches, progressing to a panel discussion covering the challenges of prescribing, diagnostics and antibiotic education, investment and building a business model for new antibiotics. The afternoon finished with a forward-looking keynote speech on innovating to secure the future of modern medicine.

This report is not a verbatim record, but a summary of the discussions that took place during the day and the key points raised. Comments and recommendations reflect the views and opinions of the speakers and not necessarily those of the Royal Society or the Academy of Medical Sciences.

Executive summary

Antimicrobial resistance (AMR) continues to grow as a critical worldwide health challenge. Pathogens are continually evolving to combat drugs given to treat potentially life-threatening diseases, rendering treatments ineffective and threatening the many advances made in fighting microbes over recent decades.

As therapeutics in current use become less effective, new approaches are urgently required. This conference aimed to raise awareness and interest for new anti-microbial advances, the challenges faced in market delivery, and their appropriate use in healthcare systems.

Key points taken from the conference included:

- **Collaboration** – The COVID-19 pandemic has demonstrated the devastating impact infectious disease can have on society. It has also highlighted what governments, clinicians, industry and academics can achieve when they work together to try and solve an emergent and urgent threat like COVID-19. This coordination now needs to be harnessed to address the slower burning antimicrobial resistance challenges which are being faced and will continue to be faced for years to come.

- **Innovation** – Innovation of existing treatments is urgently required if we want to solve the problem of antimicrobial resistance. Existing agents need to be used more appropriately, and novel techniques including bacteriophage technology and natural products, need to continue to be developed to help win the war against resistance. Innovation in diagnostics is key to enable quicker and more effective diagnosis to help better treat patients, as well as innovating clinical trial design to address the non-inferiority versus superiority challenge.

- **Building a new business model** – Currently, there is little incentive to develop new agents as the cost of development exceeds return on investment. New business models and impactful push and pull incentives are required to encourage the development of new agents and technologies. Introduction of a new trial reimbursement and procurement model from the National Institute for Health and Care Excellence (NICE) into the National Health Service (NHS) is an excellent starting point to test new models for sustainable funding of antimicrobials in the long term.

"There are headwinds present in the AMR space, but something we can rely on is the dedication and passion of the AMR community to help combat this major problem that we all face."

Dr David Powell, Summit Therapeutics.

"It is essential for academics to consider the issues of bringing new antibiotics to market in addition to selecting a protein which makes an excellent target for antibiotics."

Professor Jeff Errington FMedSci FRS, Newcastle University

"By enabling pharma, diagnostics and the academic and public health sectors to collaborate, there has been an increase in productive research and delivery of research outputs to patients."

Dr Flic Gabbay FMedSci, tranScrip Partners

Antimicrobial optimisation: research priorities, advances in innovation and lessons from COVID-19

Professor Alison Holmes OBE FMedSci, Imperial College London, outlined the importance of looking at how existing antimicrobial agents can be optimised to address the global challenge of antimicrobial resistance with a particular focus of innovation in technology. Considering AMR in the context of the COVID-19 pandemic was also covered.

The optimisation of the use of existing antimicrobial agents, without compromising access, will be necessary to address the challenge of AMR. However, there is significant funding inequity between the research and development for new drugs and the implementation and efficient use of existing agents in the AMR research landscape.[1] Four research priorities were identified for optimising antimicrobial use, namely: policy and strategic planning; medicines management and prescribing systems; context, culture and behavioural research; and technology innovation to optimise prescribing. Such technology innovation includes opportunities in personalised prescribing and dynamic dosing as well as the use of data and artificial intelligence (AI) to support decisions about prescribing.

The right dose, right now

Responses to antimicrobial drugs vary between patients as well as in the same patient over time. Standard dosing schemes do not account for this variability and the suboptimal use of antimicrobial drugs can increase the chance of antimicrobial resistance and may lead to therapeutic failure in the patient. With consideration of polypharmacy and co-morbidities, personalised dosing involves tailoring drug dose to a particular individual, while dynamic dosing tailors the dose based on the current state of the patient. Personalised and dynamic dosing present an opportunity to optimise antimicrobial drug use and improve patient outcomes.

Obtaining data for personalised and dynamic dosing is difficult, and has multiple logistical issues, such as the timing of samples, assay validity, equipment and staffing costs, and delays in reporting. To achieve personalised and dynamic dosing, data needs to be tailored to the individual, obtained dynamically and in real time, ideally using non-invasive techniques.[2] There is the potential to utilise closed-loop control for precision antimicrobial delivery, as already validated in the control of diabetes by individualised insulin delivery. Research has shown that microneedle electrochemistry sensing and biosensor technology can improve drug monitoring and provide real-time continuous antimicrobials in a minimally invasive fashion and with no requirement for blood sampling.[2]

Integrating data to provide decision support

To optimise the use of antimicrobial agents, clinicians require not only access to individual technological innovations in diagnostics and dosing, but also useful decision support tools. Currently, existing decision support systems fail to consider variation between individuals, dose optimisation, and physician/patient engagement. The lack of co-design with physicians and patients means that applicability in a clinical setting may be limited. To maximise the potential of technological innovations in diagnostics, surveillance and dosing, decision support systems should integrate relevant, standardised data from various sources, including at an individual, hospital-wide and population level, and make it available to the clinician at the point of care. Such data integration may benefit from machine learning and artificial intelligence approaches to identify patterns and risk factors, and to make evidence-based recommendations. However, it is important to ensure that the data fed into decision support systems is representative of the patient population otherwise recommendations may not be applicable to or even safe for the patients, which could worsen health inequalities.

COVID-19 and AMR

The critical need for optimising antibiotic use has been reinforced during the COVID-19 pandemic. In acute care settings, only a small percentage of hospitalised patients had confirmed bacterial co-infection with COVID-19

1   Charani E *et al* 2021 Optimising antimicrobial use in humans - review of current evidence and an interdisciplinary consensus on key priorities for research, The Lancet Regional Health – Europe 7, 100161 (see https://doi.org/10.1016/j.lanepe.2021.100161, accessed 30 July 2021)
2   Rawson et al 2021 Optimizing antimicrobial use: Challenges, advances, and opportunities, Nature Reviews Microbiology (see https://doi.org/10.1038/s41579-021-00578-9, accessed 30 July 2021)

(~6-8%), but 72% were on antibiotics.[3] The impact of this over-prescribing on antimicrobial resistance is a complex picture. When considering all inpatients in North-West London hospitals during the first COVID-19 wave, there was an increase in a variety of multi-drug-resistant organisms and blood culture contaminants,[4] alongside significant decreases in infection with *Enterobacterales bacteraemia, particularly E. coli.*

However, the effect of the COVID-19 pandemic on antibiotic prescribing is context-specific. While prescribing in acute care settings increased, there has been a significant reduction in community antibiotic prescription since the start of the pandemic (Figure 1).[5] This may in part be due to reduced transmission of infections due to COVID-19 restrictions as well as fewer people seeking out primary caregivers during lockdowns. There is a need for urgent investigation into the potential unintended consequences of reduced prescribing, such as undiagnosed and untreated infections, and the shifting patterns of community-onset infections and AMR. The differences between the acute care and community settings emphasise the need to have a whole health economy perspective when considering antimicrobial resistance, including understanding the dynamic context and the direct and indirect impact of changing practices on the population not infected by COVID-19.[2]

Many developments during the pandemic may be harnessed to help tackle AMR. For example, public awareness and acceptance of diagnostic testing has increased, which could be leveraged to improve AMR diagnostics and surveillance, supporting appropriate prescribing. Furthermore, during the pandemic, the UK has seen unprecedented regulatory agility in approval and uptake of new technologies and approaches. This could set a precedent for rapid uptake of innovations in technologies, therapeutics, data linkage, diagnostics, and collaborative trials to help mitigate AMR. There is a valuable opportunity to apply lessons learned from the COVID-19 pandemic response to address the outstanding challenges facing AMR research and policy.

FIGURE 1

Data from General Practice in North-West London showed reduced antibiotic prescribing, which was maintained beyond the two COVID-19 waves.
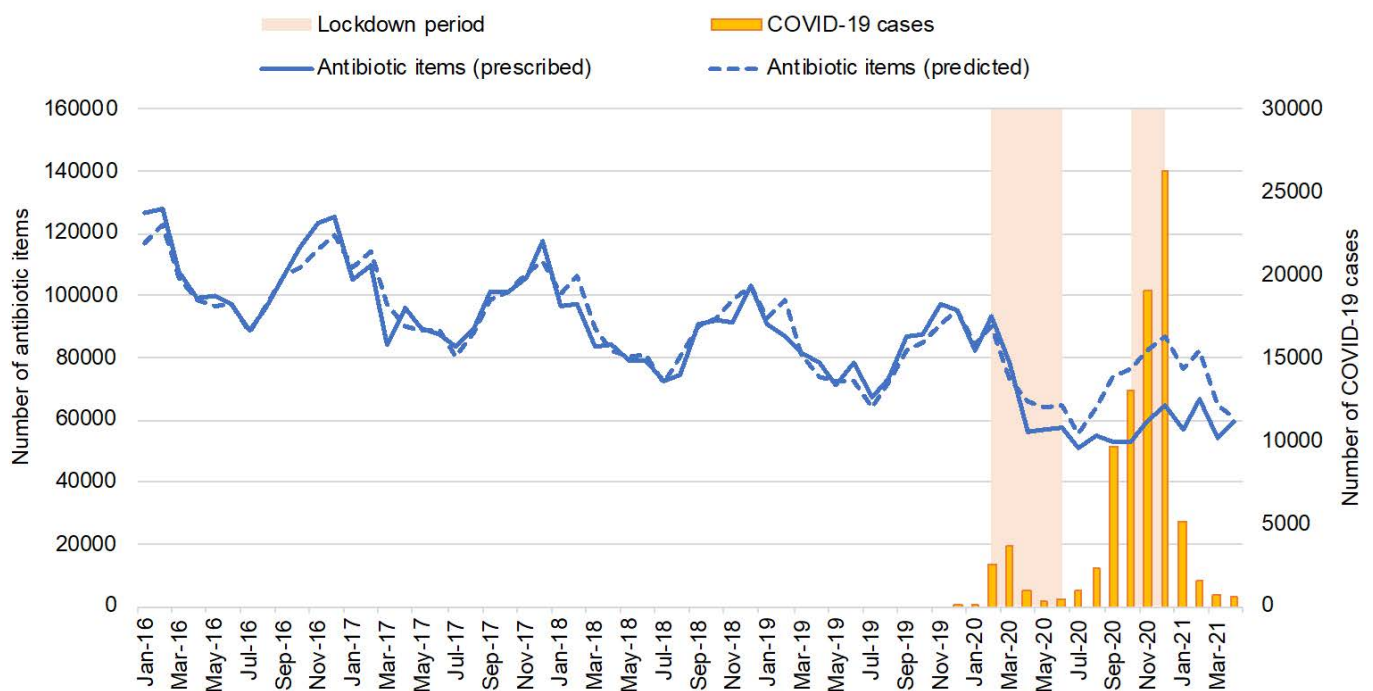
The future of AMR reimbursement: what types of products will succeed?

Dr John H. Rex, F2G Ltd, covered the issues associated with the industrial development of new antimicrobial agents, the necessity for pull incentives independent of actual antibiotic use, and the far-reaching safety net that antibiotics provide to society.

Non-inferiority vs superiority design

All clinical trials for antimicrobial agents meet one of two possible designs:

- **Superiority studies** – trying to prove the response of an investigational product is superior to a comparative agent.

- **Non-inferiority studies** – attempting to prove the response of an investigational product is not inferior to a comparative agent.

Superiority studies are generally preferred as the results are unambiguous; however, non-inferiority study design allows for new drugs to be developed before old drugs fail completely. By insisting on clinical superiority before approving new agents, progress only occurs when the pipeline becomes inadequate. Therefore, non-inferiority design acts as the future proofing tool by allowing drugs to be developed before they are needed and before AMR renders current drugs ineffective.

Developing new drugs

The standard pathway for developing new drugs involves undertaking two initial trials. Firstly, a non-inferiority study is undertaken against a good comparator drug, where both agents are predicted to be active. This is the foundation study which provides core demonstration of efficacy, as well as safety and pharmacology information. In parallel, a second trial explores the effectiveness of a novel compound against important multi-resistant pathogens. This second study is key and gives an idea about *in vitro* prediction of susceptibility compared to pathogens that are resistant to other drugs.

Narrow-spectrum antimicrobial agents target rare, multi-drug resistant pathogens. The challenges of developing narrow-spectrum agents include problems surrounding the price, speed, regulatory hurdles, and the strength of the evidence provided from trials. Diagnostics are critical for the effective use of narrow-spectrum agents; however, practical issues including screening for rare pathogens and making tests continuously available, mean the implementation of diagnostic testing is as important as the existence of a validated test for a particular pathogen.

Agents that augment

Using a drug that improves the benefit to patients, when used alongside an active companion drug is an exciting concept. However, the combination must be proven to be better than the current standard of care (SOC), which is problematic because of the lack of room for improvement with the existing SOC for bacterial infections – an antibiotic either works completely or only partially and resistance emerges. Considering different endpoints may be one approach, such as the benefit of a novel agent for wider society – i.e. in preventing the emergence of resistance – but this is problematic as current metrics focus on benefits to an individual and not society. Finally, this is not solely a regulatory problem, regulatory agencies are simply the first to draw out the issues such as cost and feasibility, with further problems developing downstream.

Antibiotics are the fire extinguishers of medicine

Whilst antibiotics are not in continual use to prevent disease, they are present in the background in case of disaster. This is much the same as fire extinguishers, which are used to prevent devastating fire outbreaks. By preventing the outbreak of disease and fire respectively, antibiotics and fire extinguishers provide a safety net for civilisation. It can be difficult to conceptualise the preventative value of antibiotics to society to justify their value even when they are not in use however, using COVID-19 as an example, if a molecule had been developed prior to the pandemic and was able to contain the outbreak, the value to the global community would have been enormous, much like the value of the antibiotic safety net.

The total cost of developing an antibiotic with ten years on the market is estimated to be $1.7 billion[2,3]. Currently, there is no way of obtaining usage-based income to recover the costs of drug development, with new antibiotics often generating less than $25 million/year in sales. As the monetary reward is so low, there is little incentive to develop new antibiotics. Bringing new agents to market requires push incentives, such as grants, and pull incentives which are awarded upon successful approval, independent of actual use. There are now multiple global calls for pull incentives[4] with the United Kingdom responding with a subscription model pilot and United States introducing the PASTEUR Act.

There needs to be a continued mental shift towards the recognition of the societal benefit of providing pull incentives that are independent of use, therefore encouraging small companies to commence clinical trials and develop new, effective antibiotics.

"Antibiotics are the fire extinguishers of medicine, and like other infrastructure, we must buy them in advance."

Dr John H. Rex, F2G Ltd.

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2   Wouters J et al 2020 AMR.Solutions: Melinta, Part 2 / Bankruptcy Is Not The End / Post-Approval Costs For An Antibiotic, JAMA 323, 844 – 53 (see https://amr.solutions/2020/01/07/melinta-part-2-bankruptcy-is-not-the-end-post-approval-costs-for-an-antibiotic/, accessed 31 August 2021)

3   AMR.Solutions: Mandatory Reading: Alan Carr's Jan 2020 Antibacterial And Antifungal Market Review (see https://amr.solutions/2020/01/28/mandatory-reading-alan-carrs-jan-2020-antibacterial-and-antifungal-market-review/, accessed 31 August 2021)

4   US: PACCARB (https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf) and PASTEUR Act (https://www.congress.gov/bill/116th-congress/senate-bill/4760/text

Session 1

Novel research and approaches

The demise and rise of phages as therapeutic antibacterial agents

Dr Heather Fairhead, Phico Therapeutics, discussed how engineered bacteriophages (phages) are leading the way in exemplifying phage therapeutics in rigorous clinical trials, and how phage technology is providing an alternative paradigm for treating resistant infections.

Bacteriophages are viruses that infect and replicate inside bacteria, and therefore they have the potential to treat bacterial diseases. A cocktail of wildtype phages are often used to treat infections due to each phage's narrow specificity. More recently, phage lysins – biological agents that cause bacteria to burst – are presenting new therapeutic options, with the potential for engineered phages that can act as delivery vehicles for antibacterial agents.

SASPject bacteriophage technology
Phico Therapeutics has developed SASPject bacteriophage technology to combat growing antibiotic resistance. SASPject are engineered by inserting the SASP (small-acid soluble spore protein) gene into the bacteriophage DNA. The engineered phages detect and bind to harmful bacteria in the body, injecting the target bacteria with phage DNA and the SASP gene. The SASP gene then instructs the bacteria to produce SASP proteins, which then bind to bacterial DNA, contorting and irreversibly damaging the DNA. Bacterial death occurs independent of any mutations in the DNA, so there is very little chance of resistance developing.

By modifying bacteriophage host receptor binding domains, which allow the phage to recognise a bacterium of interest and increasing the host range, cocktails of bacteriophages can be avoided, and the phage can be tailored to target specific bacteria. In time, phages with different host receptor binding can hopefully be combined to tackle co-infections.

Phico Therapeutics is currently focusing on serious infections with few existing treatment options, including *Pseudomonas aeruginosa,* which has up to a 50% mortality rate. SASPject has been rapidly active (Figure 2) against 90% of geographically diverse *P. aeruginosa* strains, with 53% of those strains being multi-drug resistant. Additionally, there is no geographical area where *P. aeruginosa* is not being targeted effectively, which allow the phage to recognise a bacterium of interest giving confidence that a particular resistance profile is not likely to expand.

An alternative to antibiotics
Phages present an alternative and biological means of killing bacteria that is targeted, and precision engineering is enabling the use of phages to become more commercially viable. Multiple robust clinical trials are now urgently needed to help realise the full potential of phage therapeutics. Engineered phages offer the opportunity to improve on the best wildtype phage that nature can offer, and engineered phage technologies are leading the way in establishing the clinical credentials of phage therapy.

FIGURE 2

An in vitro kill curve showing the rapid nature of SASPject technology when treating P. aeruginosa.
Similar results are observed with other targeted bacteria, including Staphylococcus aureus.
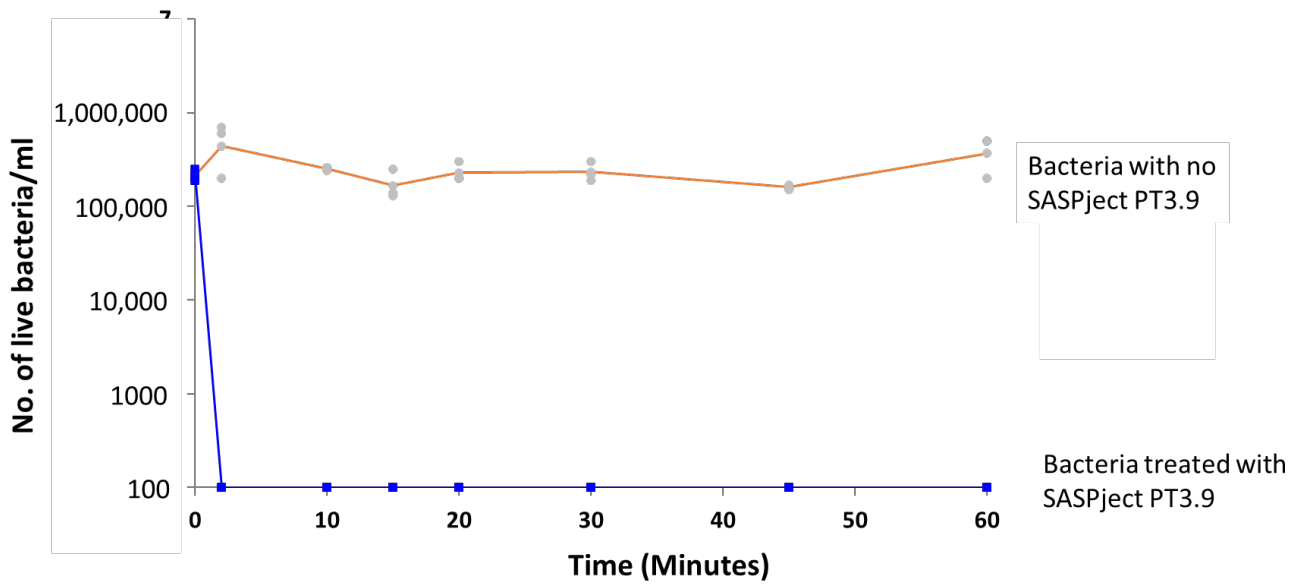
Mining biosynthetic pathways for new antibiotics

Professor Gerard Wright, McMaster University, introduced the antibiotic discovery void, as well as using examples to illustrate phylogeny and genome mining as methods for discovering antibiotics.

There has been an antibiotic discovery void since the 1980s and the era of target-based drug discovery and combination chemical libraries. Most useful antibiotics are natural products rather than synthetic molecules, having been tailormade during hundreds of millions of years of evolution. Since the golden era of antibiotic discovery, it has been increasingly difficult to find new antibiotics with desirable characteristics. However, it could be time to revisit the discovery of natural antibiotics using genomic and synthetic biology.

Using phylogeny to find antibiotics

The genetic information required to make antibiotics is almost always found in the region of bacterial DNA identified as biosynthetic gene clusters (BGCs). Within the cluster there are several essential genes, including resistance genes, enabling the bacteria to protect itself against antibiotics. The resistance gene within the BGC can then be used to find antibiotics with new modes of action.

Professor Wright's laboratory collected BGCs to build phylogenies which in turn could be used to identify divergent clades – groups of organisms with a common evolutionary ancestor – and resistance genes. Certain phylogenetic branches were associated with known resistance mechanisms which were found to be active against common glycopeptide antibiotics such as vancomycin. Branches with unknown resistance mechanisms were then investigated, and a novel antibiotic, corbomycin was identified, in addition to the previously discovered antibiotic, complestatin. When used separately to treat gram-positive *bacillus subtilis,* both were found to contort bacteria, which resulted in inhibition of bacterial cell division, suggestive of a new mode of action.

ClpP as an antibiotic target

Unpublished data is looking at ClpP, or ATP-dependent Clp protease proteolytic subunit, as a possible antibiotic target due to their presence in BGCs and its potential to be a resistance mechanism. Target-directed genome mining was used to identify a family of ClpP-associated BGCs, *Streptomyces cattleya's* BGC was utilised to produce a molecule which inactivated ClpP (Figure 3). This candidate molecule was then synthesised and found to be carbonate-like, with ClpP crystal structures showing all seven monomers within the heptamer were in an inactive state, demonstrating complete ClpP inactivation by the identified molecule.

FIGURE 3

The graph on the left shows an enzyme assay where the candidate molecule being produced inhibits ClpP completely. The mass spectrum on the right shows the molecule is increasing the mass of ClpP, suggesting inhibition results in covalent modification of ClpP.
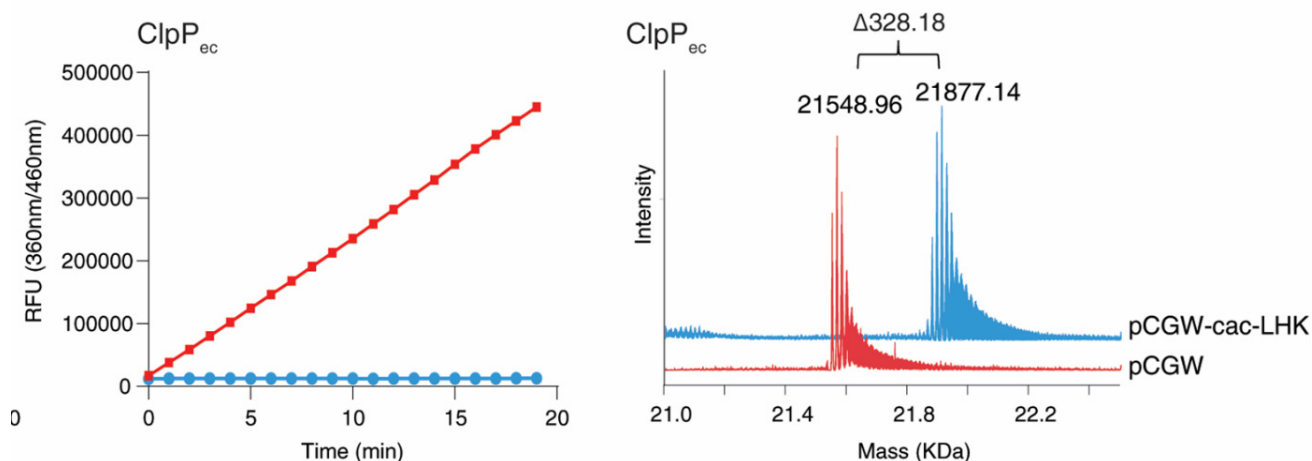
Biosynthetic mining and the future

The above are just two examples of using genome mining and phylogeny to identify new molecules, indicating there is an abundance of chemical diversity yet to mine. This is an exciting time to look for new molecules using new strategies which will hopefully reboot the scientific strategies for discovering antibiotics.

"It is now possible to use phylogeny and genome mining to find novel, interesting antibiotics with new modes of action

Professor Gerard Wright, McMaster University"

How can novel clinical trial designs address challenges in evaluating antimicrobials for multi-drug resistant organisms?

Professor Sarah Walker FMedSci, University College London, covered how clinical trials can be re-designed to specifically address challenges in evaluating antimicrobials for drug resistant organisms.

Multi-drug resistant bacterial infections result in high morbidity and raise a lot of questions including what drugs should be used and in what combination. Randomised trials provide the most robust evidence because they control for known and unknown confounders. However, it is argued randomised trials are not being undertaken in multi-drug resistant bacterial infections in either regulatory or academic settings, and therefore much evidence comes from observational studies which raised questions regarding control of confounding.

Trials in multi-drug resistant bacterial infections

The CARE trial tested plazomicin primarily in bloodstream infections and pneumonia. It screened 2,000 patients over two years and randomly assigned only 39 (2%) patients to plazomicin versus the comparator, colistin. A parallel study of plazomicin versus meropenem for complicated urinary tract infection (cUTI) screened 640 adults over nine months and randomised 609 (95%) patients but had very low mortality overall (0.2%). This raises the question whether it is acceptable to extrapolate from cUTI to all serious infections, as regulators including the FDA have done.

In another trial, 802 adults were screened over three years with 406 (51%) patients randomly assigned to colistin monotherapy or colistin plus meropenem[5]. The conclusion of the trial found there was no significant difference between colistin monotherapy and combination therapy, even though clinical failures by 14 days were numerically lower in the combination group, and failure rates were 79% with monotherapy and 73% with combination therapy. This would suggest a potential option could have been rejected simply because the trial turned out to be underpowered (targeted a 15% risk reduction), highlighting yet another problem in current clinical trial design.

The problem with standard of care (SOC)

SOC implies using one regimen as a standard for all, simultaneously maximising good outcomes and minimising bad outcomes. This is problematic as resistance genes are generally carried on variably present genetic mobile elements[6], meaning there is not a consistent pattern of cross-class resistance. Additionally, many antimicrobials have important contraindications, meaning a "one treatment fits all" SOC approach is simply not appropriate in many settings. We therefore need to extend past a single SOC which currently encourages resistance, and instead focus on driving diversity in antimicrobial therapeutics to fight against AMR.

5   Paul M et al 2018 Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial, The Lancet Infectious Diseases 18, 391 – 400 (see https://doi.org/10.1016/S1473-3099(18)30099-9, accessed 30 July 2021)

6   Genetic mobile elements are genetic material that can move within a genome, or that can be transferred from one species or replicon to another.

PRACTical designs

The Personalised randomised controlled trial design (PRACTical) differs from a traditional platform design as it does not incorporate SOC, with each patient randomised between a subset of regimens that differs from patient to patient. PRACTical design focuses on identifying which treatment will provide the greatest probability of success, whilst avoiding the worst regimen, that is essential in the world where antimicrobial diversity is important (Figure 4). This reflects the clinical compromises that clinicians make continuously eg balancing personalised decisions for each individual patient with efficacy, toxicity, resistance, availability, and cost. Utilising PRACTical designs enables quantification of these trade-offs, avoiding the worst possible treatments for patients.

> "The current single comparative trials are not designed to identify what the best regimens out of the available options are, and I would argue this is simply because standard of care does not exist for antimicrobial treatment."
>
> Professor Sarah Walker FMedSci, University College London

FIGURE 4

PRACTical aims to avoid the worst possible treatment for patients in terms of cost and mortality, compared to the SOC approach which focuses on finding the best approach on average across all patients.
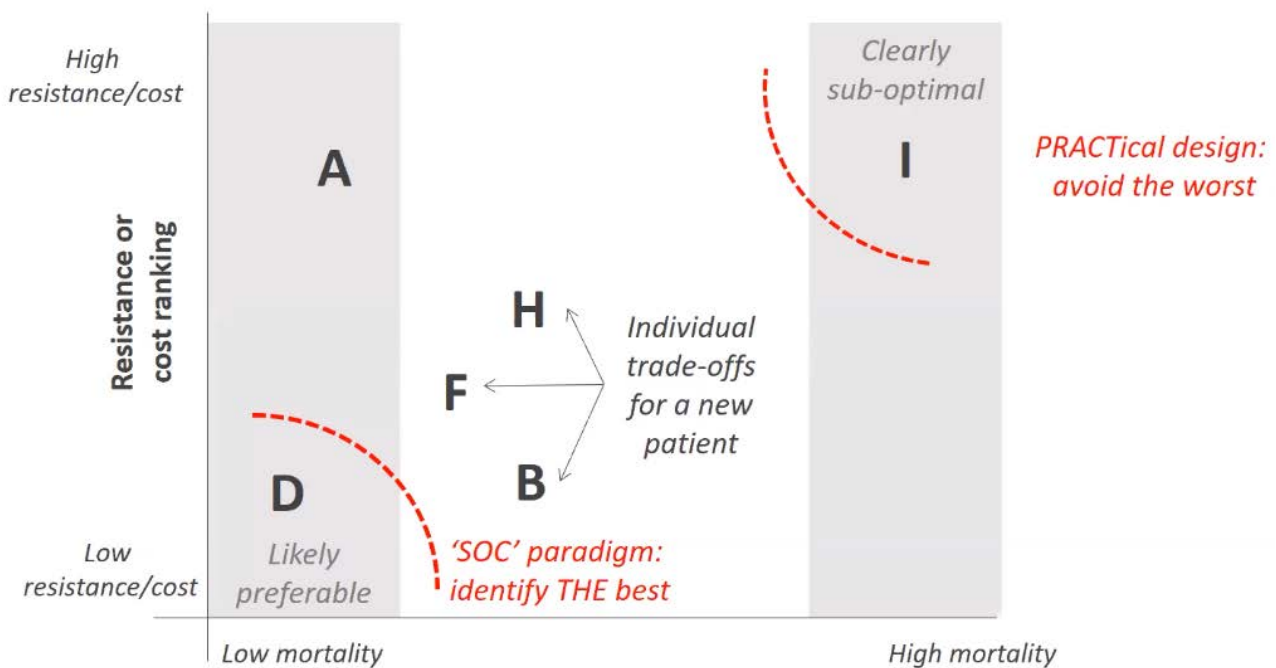
Innovation in Point of Care Diagnostics

Dr Tina Joshi, University of Plymouth focused on AMR, links to climate change and the importance of encouraging and investing in new, feasible, long term approaches to tackle AMR.

Innovation is about introducing novel developments, not reapplying old methods, and ensuring novel ways of thinking to generate a wide range of new solutions. Antimicrobial therapeutic use tends to result in resistance, and therefore solutions to AMR need to be long term as well as ensuring antimicrobial prescribing is rationalised. There have been minimal improvements in some areas of AMR with detection lagging behind discovery, and therefore innovation of diagnostics is urgently required to help beat AMR.

Antimicrobial resistance and climate change

AMR is just as much of a threat to the human species as climate change. As temperatures increase, the ability for certain diseases to transmit and proliferate increases, which is closely linked to use of diagnostics, and to transmission in low to middle income countries (LMICs). Diagnostics must be implemented in LMICs - not just in high income countries such as the UK - if we want to stop the spread of prolific diseases such as tuberculosis and malaria. When looking at AMR and climate change together, it presents a greater challenge where multifaceted solutions are required, especially as the population increases and so does the ability for AMR genes to spread.

Rapid diagnostics

Rapid diagnostics enable healthcare staff to tailor appropriate antimicrobial treatment regimens. Diagnostics are also required to reduce the incidence of transmission, allow scientists time to discover new antibiotics, and help rationalise antimicrobial use; however, no rapid diagnostic has yet gone to market with the aim of rationalising antibiotic use at the point of care (POC).

Rapid diagnostics is often a blanket term; however, niches of rapid *in vitro* diagnostics exist, including:

- **Hospital bench-top diagnostics** – Often cartridge based and employed in hospital laboratories, providing results within 20 to 90 minutes which leaves some way to go before being considered truly "rapid" and meet the target of 10 minutes.

- **POC diagnostics** – available in general practice surgeries as non-specific biomarker targets, raising the question: are they are specific enough for AMR detection?

- **Handheld technologies** – currently in development as a molecular test which meet the POC niche and considers the end user.

Innovation in POC Diagnostics

Molecular POC diagnostics, incorporating DNA/RNA extraction coupled with biosensor technology are currently the focus of development. There is an unmet need in diagnostic technology, where easy-to-use devices with minimal training are required, whilst ensuring diagnostics are truly rapid with sample to result in 10 minutes. Innovation is now required to meet the end goal of producing a sensitive, integrated, molecular and portable POC diagnostic, whilst overcoming the barriers of translating diagnostics to the market.

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"When developing an innovative diagnostic solution for AMR, cross-disciplinary research is essential to providing feasible and tangible solutions."

Dr Tina Joshi, University of Plymouth

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Antimicrobial resistance: developing and testing innovative models for the evaluation and purchase of antimicrobials

Professor Colm Leonard, NICE, and David Glover, NHS England, covered the selection process, evaluation framework and payment model for a novel, innovative payment model for antimicrobials.

NICE and the NHS are testing an innovative payment model that reimburses companies for antimicrobials based primarily on their value to the NHS as opposed to volumes used. To succeed, there needs to be an agreed health technology valuation framework and complete value assessment of the products, as well as an agreed payment framework leading to successful negotiation of payments. Pull incentives such as this novel subscription model being tested in the UK are required to stimulate companies to increase investment. Findings from the project will be used to inform the future policy for evaluating and purchasing antimicrobials in the NHS.

Selection process
The subscription model is being applied to two antimicrobial products - cefiderocol (Fetcroja), and ceftazidime with avibactam. The selection process involves a formal procurement tender with a contract for the supply of antimicrobials. Development involved engagement with industry and international stakeholders, with the payment model largely based upon output from an industry-government joint working group. The criteria for selection were as follows: ensuring the company is legitimate, able to continue operation, and able to fulfill selection requirements; and evaluation of clinical benefit including consideration for the unmet need, degree of novelty and cost of the product.

Evaluation framework
The evaluation framework is very different to normal NICE technology appraisal, with the appraisal aiming to capture additional attributes of value, including spectrum, transmission and enablement, not just the direct health effects to patients. When finishing the project, there needs to be more than just a framework for looking at antibiotics differently to other pharmaceuticals, with the requirement for valuation principles to be shared and incorporation of de-linked payments.

There are difficulties modelling antibiotics and clinical trials, including the variability of standard care and the presence of an uncertain evidence base. As a result, a pragmatic approach in the evaluation is being undertaken, defining high-value clinical scenarios where the product has the greatest potential for addressing unmet clinical need or beneficially impacting public health.

Payment model
The principle of the model is that companies are paid for antimicrobials based on the estimated value of benefits to patients and the NHS rather than payments based on volumes used. Annual payment removes the link between usage and payment, with contracts being set up for agreed volumes of product with specified delivery dates. This should give some predictability to companies, which in the long term should encourage more research and development in the antimicrobial therapeutic space.

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"We are not just looking at the direct health benefit to patients, we are also trying to identify additional attributes of value such as spectrum, transmission, enablement, diversity and insurance value."

Professor Colm Leonard, NICE

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"We hope this novel contract will provide the foundations for routine supply of antimicrobials in the NHS."

David Glover, NHS England

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Session 2
Panel discussion

Challenges of prescribing, diagnostics, antibiotic education, investment and building a business model for new antibiotics

This panel discussion, chaired by Dr Flic Gabbay, tranScrip Partners, comprised Dr Erin Duffy, CARB-X; Dr Adam Zerda, Becton, Dickinson and Company; Professor Angharad Davies, Swansea University Medical School; and Dr Michael Gutch, Entasis Therapeutics. The panellists commenced by introducing their specialisms and providing key points for discussion, including issues associated with prescribing and diagnostics, as well as ways to improve investment opportunities and business models for new antibiotics. Antibiotic education was also touched upon.

Prescribing practices

- Decisions about prescribing antibiotics are complex, in part due to the large number of antibiotic agents available in addition to the complexities imposed by rising antimicrobial resistance.

- Antibiotics are unique agents among drugs because the prescriber not only has to weigh up the potential benefits and harms to the individual patient, but they must also consider the impact on the community and future patients.

- Clinicians tend to focus on individual care rather than broader public health considerations, with some studies showing individual risk being prioritised over population risk.

- Clinicians may be understandably hesitant to 'not prescribe' in case a bacterial infection is later confirmed, at which point it could be too late for the patient.

- The development of mobile, real-time decision support systems to integrate data from various sources and make evidence-based prescribing recommendations at point of care would support clinicians to prescribe antimicrobial agents more effectively.

- Focusing on prescribing practices for narrow-spectrum agents could result in the potential to generate greater efficacy and safety when prescribing antibiotics, as well as producing a more targeted treatment with fewer side effects.

Education and training in microbiology

- Clinicians need further education and training, so they have the understanding to underpin and enable effective antibiotic prescribing decisions.

- Prescribers need an understanding of how to interpret microbiology reports, which unlike many blood science reports, are numerically based and need clinical interpretation to recognise contaminants and pathogens versus the normal microbiota.

- Healthcare professionals suffer from lack of training in antibiotic usage, prescription and the biology surrounding microbes; on average, only 5% of 5000-hour medical school courses are spent on clinical microbiology, haematology, and biochemistry, reflecting the massive pressure on time in the medical school curriculum.

"Prescribing antibiotics is difficult for junior doctors, not only because of the variety of antibiotics available, but due to the requirement for consideration of the individual patient and the wider community."

– Professor Angharad Davies, Swansea University

"Rapid uptake of a new antibiotic to market requires them to be available on automated susceptibility testing diagnostic platforms, which is greatly aided by commencing pilot work and developing partnerships early."

Dr Erin Duffy, CARB-X

- Incorporating antibiotic prescription and stewardship topics in exams for medical students and within the medical school curriculum itself will help improve microbiological understanding and antibiotic prescribing practices.

- The introduction of the General Medical Council's Medical Licensing Assessment – which all medical students will have to pass to practice medicine in the UK from 2024 – could present an opportunity to prioritise education in antimicrobial resistance and stewardship.

Diagnostics

- Innovation of diagnostics will enable prescribers to better assess and treat infections, as well as more effectively identifying the drugs to which the infection is resistant or susceptible.

- In addition to providing better patient outcomes, diagnostic innovations will enable effective antibiotic use and so reduce the emergence of antimicrobial resistance, protecting the whole community.

- Testing is often more expensive than the antibiotics themselves, so more needs to be done to promote the societal value of using diagnostics, even where there is an additional direct cost.

- Diagnostics are vital to the adoption and useful implementation of new antibiotics, especially narrow-spectrum antibiotics where the specific pathogen needs to be identified quickly.

- The time from sample collection to antimicrobial agent selection and delivery should be appropriate to the urgency of the illness as the time to diagnosis could be the difference between life and death.

- Increasing the speed of diagnosis can involve innovations in sample collection, testing logistics eg sample transport between sites, quicker diagnostic tests, swifter reporting to the clinician, developing mobile bedside diagnostic technology and POC testing.

- Innovations in rapid POC diagnostics that can distinguish between viral and bacterial infections could lead to a reduction in unnecessary antibiotic prescription, whilst expediting the delivery of patient treatment.

- COPD and asthma viral exacerbation can often lead to secondary bacterial infections. Health Canada is currently seeking to develop a test that can differentiate between viral and bacterial infections, which would allow the correct treatment for each illness to be swiftly identified.

- Currently, data from diagnostics is often being used ineffectively as clinicians are not able to access and act on these data easily.

- To maximise the potential of current and future diagnostic technologies, it will be essential to integrate diagnostic results with other data in decision support systems so that clinicians have all the relevant information they need at point of care.

- Methods are now being developed to better connect electronic health records with other health data sources so physicians can have access to the full set of relevant information more quickly.

Investment and building a business model for new antimicrobial agents and related technologies

- There is currently a lack of market interest in the development of antimicrobial agents and technologies due to uncertainties in the market.

- Return on investment in antimicrobials is not in parity with return on investment in other therapeutic sectors, and hence a large proportion of large pharmaceutical companies and investors have withdrawn from the antimicrobial space.

- While there are some encouraging policies for funding and support, these are not sustainable and will not result in a sustainable pipeline in the medium and long term.

- There is currently a perceived lack of interest from many governments, in supporting development of antimicrobials, and therefore policy needs to be changed to ensure the field receives adequate recognition and funding.

- Push and pull incentives are required to encourage the development of new antimicrobial therapeutics and related technologies eg diagnostics, whereas currently they generate less money than they cost to produc e.

. . . .

"Surveillance is key and we need to ensure that new diagnostics are being used as frequently and as broadly as they possibly can be."

Dr Adam Zerda, BD

. . . .

"Antimicrobial resistance is truly a global problem, and we need to build a better business model to allow companies to remain sustainable to innovate against this problem."

Dr Michael Gutch, Entasis Therapeutics

Innovating to secure the future of modern medicine

Professor Dame Sally Davies DBE GCB FMedSci FRS, UK Special Envoy on Antimicrobial Resistance for the UK Government reflected on key global advances in antibiotic innovation, and what the world still needs to do to win the war against superbugs.

AMR is every bit as complex as climate change so politicians need to be made aware of this by researchers providing case studies, ideas for intervention, evidence to inform policies, and by ensuring facts are told as relatable stories. We can isolate the problem but identifying how to make the changes needed is vastly more difficult. For example, rapid diagnostics are an essential part of enabling change, and they need to be shown to not only work when needed, but also to ensure they are not more expensive than the antibiotics themselves. Additionally, universal health coverage (UHC) must address more than sickness and treatments, it must embrace prevention and for health management, involve diagnostics at its centre.

Innovation

The need to innovate is strikingly obvious in research, but we also need innovation in surveillance and policy, as well as in behaviours, and funding for health systems that impact behaviour.

This year, the current global clinical antibiotic pipeline has 43 antibiotics and combinations with a new therapeutic entity, and 27 non-traditional antibacterial agents, demonstrating the introduction of new methods as well as innovation with old agents. Of these agents, 26 are active against the World Health Organisation's priority pathogens, but only two are active against multi drug resistant gram-negative bacteria. What is more, of the 11 newly approved antibiotics, since 1 July 2017, only two have demonstrated clinical benefits over and above existing treatment, really highlighting the need for rapid innovation.

When the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act[7] is hopefully established in the US, it should ensure the introduction of a de-linked payment model for antimicrobial treatments. It is hoped, alongside the NHS Pilot, that it will show other countries innovative approaches to pay for antibiotics, giving healthcare systems the best chance of treating us all.

Vaccines

Vaccines have always provided a sustainable impact, and so promoting greater and more widespread use is essential. Vaccines need to be made affordable to benefit low- and middle-income countries, with high income countries leading the way as vital drivers to support the global ecosystem.

Vaccines are a vital part of the toolkit for solving AMR, not only in humans, but also in animals, where vaccines allow for an increase in protein production without the use of antibiotics, therefore preventing resistance developing. In humans, one example from South Africa showed that there was a 67% reduction in penicillin resistant invasive pneumococcal disease in groups that received the pneumococcal conjugate vaccine. This evidence is vital for the value proposition when trying to explain why lots of children and older people should be vaccinated.

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"Is important to remember that innovations are only meaningful when they are used appropriately."

Professor Dame Sally Davies, UK Special Envoy on Antimicrobial Resistance for the UK Government

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7   PASTEUR Act: BON20468 (senate.gov)

AMR and climate change

More than 70% of antibiotics used are passed out into the environment by animals and humans. Last year, the world's largest study of antibiotics in river water found that over two thirds of 700 samples around the globe contained antibiotics. Most of the high values were found in Asia and Africa, and there was an extreme case of metronidazole found in a river in Bangladesh where concentrations were three times higher than the AMR Industry Alliance suggests is a safe environmental concentration. It is promising to see that the G7 is now committed to work with the AMR Industry Alliance to build knowledge about AMR and the environment and to think about manufacturing discharge levels and methods on how to measure them.

The way forward

Not enough people know of the danger of AMR, with only 19% of UK adults saying they think it is a problem, and so we need patients and experts to tell the AMR story much more publicly to raise greater awareness. Data are also required to strengthen our health systems. One example is the founding of the Fleming Fund, which aims to help to fund laboratories and bring evidence and people together to encourage action against drug resistance in countries across Africa and Asia. Going forward, we need to collaborate and share data with others, as well as taking a systematic and systemic approach, which will hopefully lead to a heather world.

"Antibiotic resistance is like a lobster being dropped into water and heated slowly – it is a silent, deadly and continuous problem, much like a lobster's imminent fate, slowly cooking on a low heat."

Professor Dame Sally Davies, UK Special Envoy on Antimicrobial Resistance for the UK Government

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For further information
The Royal Society
6 – 9 Carlton House Terrace
London SW1Y 5AG

T +44 20 7451 2500
W royalsociety.org

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For further information
Academy of Medical Sciences
41 Portland Place
London, W1B 1QH

T +44 20 3141 3200
E info@acmedsci.ac.uk
W acmedsci.ac.uk

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