

Antimicrobial resistance: environments, evolution and transmission

Networking workshops for researchers

Workshop series summary

Charles Darwin House, London, 25 June 2015

Discovery Centre for Translational and Interdisciplinary Research, University of
Dundee, 3 July 2015

MediCity, Nottingham, 7 July 2015

Organised by the

Learned Society Partnership on Antimicrobial Resistance



The British Society for
Antimicrobial Chemotherapy



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Learned Society Partnership on Antimicrobial Resistance

The Learned Society Partnership on Antimicrobial Resistance (LeSPAR) is a partnership of seven UK learned societies who have come together to support actions that can mitigate the global challenge of antimicrobial resistance. Collectively, these societies represent around 75,000 scientists.

LeSPAR aims to provide a single, unified voice and mobilise the UK's collective research community in order to enhance understanding and knowledge-sharing between academia, industry and clinicians. The group is focused on taking action, championing best practice and raising awareness of the global challenge of antimicrobial resistance.

LeSPAR will achieve these aims by:

- Supporting researchers in creating, sharing and applying knowledge.
- Organising focused events to enable networking and knowledge exchange, and to promote effective collaborations across disciplines and sectors.
- Engaging with government and funders to achieve policy and funding support for the antimicrobial research community, and connecting expertise from our membership to policy-makers.
- Assembling information on relevant resources and meetings.

LeSPAR member societies:

- Biochemical Society
- British Pharmacological Society
- Microbiology Society
- Royal Society of Biology
- Royal Society of Chemistry
- Society for Applied Microbiology
- The British Society for Antimicrobial Chemotherapy

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Summary

The Learned Society Partnership on Antimicrobial Resistance held three interdisciplinary networking workshops, which brought together researchers from all career stages, with diverse interests in fundamental and translational research relating to the evolution and transmission of antimicrobial resistance (AMR). Disciplines represented across the three workshops included biochemistry, chemistry, engineering, mathematics, microbiology and pharmacology.

AMR is a global health threat. A better understanding of how different environments and antimicrobial uses affect the evolution and transmission of resistance is key to tackling AMR. These environments include: animal and human host tissues; hospitals and urban environments; and agricultural and natural settings.

Interdisciplinary research and knowledge exchange across medicine, the biological sciences, physical sciences, engineering, maths, social sciences, agricultural and veterinary sciences will be vital for closing this knowledge gap and translating research into applications to tackle AMR.

Each half-day workshop was attended by 47–57 delegates, including academic researchers and postgraduates from across the UK. There were also delegates from the pharmaceutical industry, small and medium enterprises, funding bodies including MRC, BBSRC and NERC, and learned societies.

The workshops included invited talks from established AMR researchers and representatives of the AMR Funder's Forum¹, poster sessions, informal networking time and a structured networking and discussion session, where delegates were invited to propose and discuss topics of interest. The three workshops were:

- Workshop 1: Charles Darwin House, London, 25 June 2015. Chaired by Professor Jodi Lindsay, Professor of Microbial Pathogenesis at the Institute of Infection and Immunity, St George's, University of London.
- Workshop 2: Discovery Centre for Translational and Interdisciplinary Research, University of Dundee, 3 July 2015. Hosted and Chaired by Professor Mike Ferguson, Professor of Life Sciences and Associate Dean for Research Strategy, The College of Life Sciences, University of Dundee.
- Workshop 3: MediCity, Nottingham, 7 July 2015. Hosted by Professor Christine Dodd, President of the Society for Applied Microbiology and Chair in Food Microbiology, University of Nottingham. Chaired by Dr Dov Stekel, Associate Professor of Integrative Systems Biology, University of Nottingham.

¹ AMR Funders' Forum. <http://www.mrc.ac.uk/research/initiatives/antimicrobial-resistance/antimicrobial-resistance-funders-forum/>

Key objectives of the workshops were opportunities to network with researchers in other disciplines, keeping up-to-date with the latest AMR research and learning about AMR funding opportunities. 98% of delegates who completed the evaluation survey agreed that these objectives were met.

This workshop series summary includes the presentations (page 4) and topics and issues raised during the discussion sessions (page 6).

This summary is based on discussions during the workshop and delegate feedback. It does not purport to reproduce all discussions. Note that the messages conveyed in the summary do not represent official positions of the individual learned societies of the Learned Society Partnership on Antimicrobial Resistance.

Presentations

Invited research presentations

Introductions from the respective Chairs and invited talks at each workshop provided an overview of the importance of interdisciplinary research to tackle questions on AMR across a diverse range of environments, including the outdoor environment, clinical settings and within the host. Delegates commented on how useful and stimulating it was to hear of the diverse, interdisciplinary approaches to AMR. In some cases, the speakers posed as many questions as they answered, which served well to stimulate the later discussion sessions.

London invited presentations:

Environmental dimension of antibiotic resistance, Dr William Gaze (European Centre for Environment and Human Health, University of Exeter). William spoke about his collaborative research using genomic approaches to identify aquatic reservoirs resistance relating to waste water in the Thames catchment area and research looking at human exposure to resistant bacteria in English and Welsh bathing waters. William's group also uses *in vitro* experimental evolution approaches to study selection for resistance.

Tackling AMR in the clinic and multi-drug resistant Gram-negatives, Dr David Wareham (Queen Mary University and Barts Health NHS Trust). David spoke about multiple-drug resistant infections and the problem of AMR in the clinical environment, highlighting the role of fundamental and applied research in tackling these issues.

Engineering the built environment to address the AMR challenge, Dr Lena Ciric (Healthy Infrastructure Research Group, University College London). Lena spoke about her interdisciplinary research combining microbiology and engineering to investigate the spread of disease in the built environment and develop and test engineering solutions to reduce this.

Dundee invited presentations:

Multidisciplinary and health informatics approaches to tackling AMR, Dr Charis Marwick (University of Dundee and NHS Tayside). Charis spoke about the use of novel health informatics approaches to

investigate the epidemiology of infections (particularly *Clostridium difficile* infection) and development of resistance through antibiotic use, and the use of this research to support and evaluate changes in policy and practice.

Antibiotic resistance genotype-phenotype association: from discovery to clinical implementation, Professor Julian Parkhill FSB FRS (Wellcome Trust Sanger Institute). Julian spoke about his research using high-throughput sequencing technologies to identify antibiotic resistance determinants in bacterial populations, discussing the potential for using these to predict resistance from whole genome sequences in clinical practice, and the importance of this for antimicrobial stewardship.

Nottingham invited presentations:

Antimicrobial resistance in the outside environment: Challenges and opportunities, Dr Rachel Gomes (Faculty of Engineering, University of Nottingham). Rachel spoke about the different outside environments and environmental relationships leading to a focus and case study on the wastewater environment. Approached from a process engineering perspective, her work on pharmaceuticals and AMR in wastewater discussed process influences, treatment technologies and the complexity and granularity of this issue. Her talk highlighted the challenges the opportunities going forward including how different disciplines can best work together to address this interdisciplinary issue.

AMR in the gut environment: a modeller's view, Dr Jan-Ulrich Kreft (University of Birmingham). Jan-Ulrich – a microbiologist turned mathematical modeller – discussed the impact on resistance of discontinuing antibiotic use and the evolutionary drivers that lead organisms to become resistant.

Posters

Delegates were invited to highlight their own research during the poster session that took place over the networking lunches and breaks at the workshops, which further outlined the diverse range of research being carried out by the groups represented on the day and provided focal points for networking.

Cross-Council Initiative on AMR presentations

Delegates welcomed the opportunity to hear from Research Council representatives of the AMR Funder's Forum and the Cross-Council Initiative on AMR at each workshop. Dr Ghada Zoubiane (Medical Research Council) presented in London; Dr Adam Staines (Biotechnology and Biological Sciences Research Council) presented in Dundee; and Dr Lizzie Garratt (Natural Environment Research Council) presented in Nottingham.

The talks provided a thorough overview of the current opportunities for Research Council funding and also alluded to the desire for a longer-term commitment to funding AMR-related research.

The scientific focus of the workshops was on environments, evolution and transmission, aligning with 'Theme 3' of the Cross-Council Initiative. The Research Councils have initially focused on the outdoor

and host microbiome elements of this theme and a first call for Research Grant Outlines² was launched soon after the workshops, with a second call for Pump Priming Grants³ released in August 2015. A Town Meeting on 11 September 2015 is also included to promote these calls, where applicants will be able to discuss their proposals with funders, potential collaborators and end users².

Networking and discussion sessions

The final session of each workshop was dedicated to structured networking and discussion. Each group was selected in advance to ensure a good mix of delegates, taking discipline, career stage and sector into consideration. The first phase involved round-table introductions which were then followed by a structured discussion session. Each table was asked to come up with a single question or issue that they felt was critical to understanding AMR in real life environments.

Across the three workshops, delegates identified many scientific challenges that will need to be addressed in order to better understand and tackle antimicrobial resistance; other areas highlighted included innovation, impact and fostering research collaborations. Questions and topics proposed across the three workshops included (grouped by theme):

Scientific challenges:

- The opportunities and challenges associated with natural product discovery.
- AMR in the environment.
- Opportunities from screening old drugs and combination therapies.
- New antimicrobial drug classes and strategies.
- Rapid diagnostics that distinguish between commensal and infective organisms in samples.
- Why do certain drugs have better therapeutic outcomes? Can we achieve personalised medicine to tackle AMR?
- How many new antibiotics do we need?
- Is it too late to conserve antibiotics? Should we be looking elsewhere?
- Are the experiments that we perform in the lab relevant? Can this explain why some strains become dominant?
- Should we standardise protocols between and among labs in order to better compare results from different environments?
- Is selection for AMR happening in the environment? If so, where and how? And what are the implications for human and veterinary medicine?

² <http://www.nerc.ac.uk/research/funded/programmes/amr/news/ao-outline/>

³ <http://www.nerc.ac.uk/research/funded/programmes/amr/news/ao-pmgrants/>

- We need realistic lab-based models and model systems, including alternatives to animals, to study infection and therapeutics.
- What is resistance?

Collaboration and linking researchers:

- The need for an international consensus on stewardship.
- Encouraging, maintaining and curating open access to data. In what way can we identify and group people with a common interest in alternative approaches to antibiotics? And how to support this?

Innovation and impact:

- How long until we are able to translate research into impact? What can be done to improve this?
- Do preconceptions of funders and researchers kill off innovation?

Once the questions had been proposed, delegates were then free to join more in-depth discussions on any of the tables, followed by an overall discussion session of each question in turn. In summary, the following key topics, issues and ideas arose across the three workshops:

Research funding opportunities and challenges

The involvement of Research Councils at these meetings and promotion of the AMR Funders' Forum and the Theme 3 Town Hall meeting was very welcome. There was a desire amongst delegates to provide constructive feedback to the Research Councils and consider how to support them to ensure future funding in AMR was maintained.

Funding call timing and information

Some delegates expressed that the funding call timelines are currently too short and may act to curtail innovative or high-quality submissions. This was seen as a particular challenge for cross-disciplinary and collaborative funding applications where time is required to complete an application that involves numerous contributors. It was also highlighted that greater information from funders about the development, content and timings of calls, prior to launch would make it easier to prepare higher-quality submissions. The presentations from funders at the workshops were welcome in this respect.

Participants highlighted the importance of being primed before the call came out. For example, it was highlighted from personal experience that 18 months' planning, including speaking to companies about the possible potential for translation, can be required prior to applying for big collaborative grants.

Funding availability to early-career and cross-discipline researchers

Perceived challenges concerning access to funding for early-career researchers, and those looking to move disciplines were also discussed; this was highlighted as being important to generate innovative

research. Given the focus on interdisciplinary grants, it was suggested that more clarification about what is required from a researchers' track record would be helpful.

It was also discussed that while larger strategic funding streams and pump priming grants were important, it is also vital to prepare and support researchers, including early-career researchers and those hoping to move into the field of AMR, to submit strong responsive mode applications.

Supporting collaboration and knowledge exchange

Global action

The importance of ensuring unilateral global action and support for surveillance and stewardship activities was raised, including supporting low- and middle-income countries where surveillance and stewardship activities are more limited. The need to promote public behaviour change was also raised.

Linking academia and industry

The need to support the development of new antibiotics through funding incentives and public-private partnerships was raised at all three workshops. Delegates discussed whether the financial reward was enough to engage big pharma. In practice, the most sustainable approach may necessarily be cross-company, and cross-continent. It was noted that approaches in Europe are perhaps quite different from elsewhere in the world.

The work of the Review on Antimicrobial Resistance⁴ was raised, including the question of how the AMR research community and Research Councils could utilise the evidence and proposals put forward by the Review.

The Innovative Medicines Initiative's *New Drugs for Bad Bugs*⁵ programmes was highlighted as an important existing partnership between academia and industry.

In London, it was suggested that university engineering departments engage much better with industry, perhaps due to the applied nature of this research and a more specified career path; perhaps this interaction is something to which relevant sciences should aspire?

Building university–industry collaborations through joint postgraduate and postdoctoral funding was also discussed in London. It was noted that there was a need for postdoctoral experience in industry, but complications and costs can make securing co-funded positions challenging. However, it was highlighted that there are good schemes out there, such as the Doctoral Training Centre in Newcastle, which has a number of researchers working on antibiotic development and has strong industry links.

⁴ <http://amr-review.org/>

⁵ <http://www.imi.europa.eu/content/nd4bb>

Facilitating dialogue between academia and industry, particularly gaining access to the microbiologist knowledge base, was also highlighted as being important when generating risk assessments for new antimicrobials.

Linking a diverse research community

One of the discussions in Nottingham centred on the value of bringing together the diverse community of researchers working on alternatives to antibiotics. Participants were keen to have further cross-disciplinary meetings, such as these workshops. Research Council funding for networking would be welcome and, even more so, there is a desire for sandpit meetings where groups may be able to bid for funding. Ideas included having networking meetings at broader conferences organised by learned societies. There was a question, though, of how a conference-based event might attract a broader audience such as that present at this event, including individuals who might not normally attend such conferences.

More generally, the value of hearing what different research communities work on, what methods they use, how to assess which interventions might be most useful and how these communities could interact better, arose in discussion and conversation across all of the workshops.

Data access and exchange

In Dundee, the issue of improving the accessibility of AMR data was discussed. It was felt that more support was needed for the maintenance and long-term curation of the various databases that house AMR-related data. Improving tools to interrogate multiple databases would also be desirable.

Delegates acknowledged that many organisations and initiatives are already involved in AMR surveillance and are committed to Open Access data. However, an issue is that the data is often not linked to clinical data for ethical and data protection reasons. Whilst these considerations are important, it would be useful to be able to link individuals back to disease in order to track infection chains (e.g. MRSA outbreaks) and understand the full phenotype-genotype context.

It was also highlighted that the fight against AMR starts with the patient and individual and it is important to reassure and engage the public about the importance of collecting clinical data and how it is anonymised and used.

Delegates noted that collating and standardising surveillance data into a single global repository would be a very useful, but challenging, exercise.

Scientific challenges

AMR in the outdoor environment

A number of discussions focused on the issue of AMR in the outdoor environment. Generally, it was agreed that more fundamental research was needed to fill knowledge gaps about reservoirs of resistance and selection factors in the environment. Other specific topics discussed included:

- The current lack of environmental protection goals for AMR. However, it was noted that industry was pushing for more controls in the future, working with both regulators and the Research Councils.
- The importance of the veterinary and farming perspectives. For instance it was highlighted that Bristol University are creating a biobank of cow faecal samples as a research resource.
- Can we engineer antibiotics to break down faster in the environment?
- The relevance of looking for resistance genes in the environment (e.g. metagenomics) was discussed, given a potential lack of context to such samples.
- Appropriate disposal of antibiotics.
- What is an experimental endpoint to consider success in understanding resistance?

Limitations of lab-based research

It was noted that, overall, we do not understand the role of resistance in infection biology, colonisation and transmission as well as we should. Part of the problem is being able to create laboratory conditions that are an appropriate proxy for real life scenarios.

Media

Are laboratory culture media providing a realistic substitution for the normal physiology and metabolism of organisms? It was felt that there need to be an emphasis on better systems under development, such as synthetic sputum.

3D tissue models, utilising stem cells to create the lung environment in the lab, for example, were also discussed as an alternative to growing microbes in culture.

Culturing bacteria in current media was described as “like throwing a lion in a hotel room and observing its behaviour – sure, you could introduce a zebra and you’d observe something, but data would be missing because the environment is so artificial.”

Laboratory strains

It is becoming clear that the lab strains that have been used for years are approaching the extent of their usefulness in this area. Recent work on clinical isolates serves to confirm just how different clinical specimens can be to laboratory strains. This raises several questions:

- Should we use clinical strains?
- Is it more appropriate to use whole populations from patient or environmental samples?
- Is it important to use spatially structured populations, such as biofilms?
- Would a blend of populations be more appropriate, given that clinicians are dealing with non-homogenous infections?

- How easy would it be to get people to give up their “pet” strain? Perhaps an approach that enables us to keep our lab strains and introduce additional strains in a high throughput system would be preferable.

Experimental design and models

To really understand the biology of infection and the impact of any interventions, we need to mimic real life situations better. For example, to design anti-virulence drugs that interfere with quorum sensing, we have to know what role quorum sensing plays in infection. In the case of a *Pseudomonas* biofilm, it turns out only a small percentage of the bacterial population are using quorum sensing and it is not clear whether interfering with this process would disrupt infection treatment or prevention.

Further discussion points about experimental design and models included:

- What is a good model of a biofilm? A flow cell might be a good model for a catheter infection but in most wound infections the bacteria are stuck down and don't move.
- How much does mimicking a clinical environment matter?
- How can we consider all aspects of an environment? Testing just a single condition can't reflect the heterogeneity that is seen in real life. There was a suggestion that microfluidics could help in this respect. A single chip could test many environments using individual bacteria. It is, however, difficult to include the host as part of such a system, as human and animal tissues are made up of many different cell types.

Systems approach

AMR is the result of an evolutionary process that happens within a complex and not well-defined network. This involves microbes, water, food, soil, humans, animals and more, so taking a systems approach would help.

One theory is that antibiotics are behaving like signalling molecules and are just one of the signalling molecules amongst the many others that bacteria are responding to. It becomes necessary to consider the interaction and interplay between these hundreds or even thousands of elements in the system.

Standardising methodologies

We know that different methods are yielding different results. It's accepted that more collaboration and interdisciplinary work is desirable but we need to define:

- i. What is resistance?
- ii. What specific environment is being modelled?
- iii. Which aspects of an environment can we control experimentally?

The ability to develop controlled microcosms could pave the way for broader research on specific environments.

Databases of laboratory methodologies should be able to connect microbes and environments and enhance comparability. The use of mathematical modelling should be explored and integrated with other disciplines.

This proposed area of work would go beyond current meta-analyses.

Prescribing and diagnostics

Dosing levels

Important aspects that still need to be addressed are dosing levels and targeting of drugs, both to avoid inappropriate single prescriptions and to discourage unnecessary poly-pharmacy approaches where multiple drugs are given in the hope that one of them works. However, it was noted targeted combination therapies can be used to help inhibit resistance from developing.

Personalised medicine for AMR

Can we take a stronger holistic approach that combines information on the host, pathogen and environment, and how a drug works to narrow down the variables that affect the success of treating disease? The idea of personalised medicine for AMR was raised, with reference to how cancer research and treatment has developed over recent years.

Diagnostics

Rapid identification is very important to improve the prescription of antibiotics. Participants discussed the challenges of developing new approaches to distinguish between commensal and infective organisms in samples, such as sputum and faeces, where there are many types of bacteria. Improving databases and interrogation tools was identified as being important. It was also highlighted that diagnostics need to be designed from a clinician's perspective to be most effective.

New drugs and treatments

Combination therapies

The importance of combination therapies to help inhibit the evolution of resistance was discussed.

Beyond antibiotics

Discussions about developing alternatives to antibiotics and strategies to antibiotic drugs featured strongly at all three workshops. It was questioned whether there would be success in focusing on stewardship during antibiotic development. Research areas highlighted include:

- antivirulence therapies based around quorum sensing
- antimicrobial peptides
- evolutionary strategies (e.g. plasmid transfer, 'Trojan horse' strategies based around sociality)
- anti-resistance therapies (e.g. efflux pump inhibitors, beta-lactamase inhibitors)
- vaccines

- restoring the microbiome
- immune modulation for non-acute conditions
- probiotics

Natural products

Participants discussed routes to better facilitate discovery of new drugs from natural sources. Some of the issues raised included: the need for better collaboration between biochemists, microbiologists and soil scientists; the problem that many antimicrobial compounds have been identified, but cannot be used due to toxicity; and questions concerning patents and intellectual property. Can we also improve culturing through more rational design, by using the genotype to identify the optimal environmental requirements for a particular strain?

Opportunities to better link AMR researchers with communities working on natural products, synthetic chemistry, chemical biology and synthetic biology should be explored.

Defining resistance

Perhaps the greatest and most important challenge is to define what we mean by resistance. Do we mean genetic or phenotypic characteristics? Is resistance just the ability to survive antibiotic treatment? Are we talking about survival of a single cell or whole populations? What would be the experimental endpoint to determine that selection had occurred?

How relevant is it to look for resistance genes? We often don't know the context of the gene – you might find a couple of hundred resistance genes in the strain but are they actually conferring resistance in that particular environment? Are there phenotypic signs of resistance?

What is it that is moving into the clinical setting to cause the problems associated with AMR? Is it bacteria, genes, plasmids, integrons, insertion sequences? This is an area that needs much more research.

Outcomes from the evaluation survey

The evaluation survey (44 responses) rated the scientific lectures, talks from funders, networking opportunities and the discussion sessions highly. Three key outcomes from this series of workshops included:

Creation of interdisciplinary links and enabling research

- 84% of respondents made new professional connections.
- 65% made an interdisciplinary connection.
- 65% connected with a potential research collaborator.
- 61% learned about an area or research discipline they were unaware of before.

- 72% found ideas and information to develop their own research.
- Many respondents valued the opportunity to network across such a broad range of disciplines, and to discuss how interdisciplinary research could tackle AMR.

Providing feedback to the funders

- 58% of respondents highlighted the opportunity to hear about funding as one of their reasons for attending. The perceived lack of funding and early information about funding calls was highlighted as key issues by the research community.
- Positive comments were made about involvement of the AMR Funders' Forum representatives at the workshops; delegates appreciated funder engagement with these workshops especially to understand scope/criteria of calls.
- LeSPAR will be sharing a summary of the workshop report with the AMR Funders' Forum.

Potential areas to explore

The discussion sessions highlighted a range of potential interdisciplinary areas that funding bodies and learned societies could support the research community to explore. Some examples include:

- Better understanding of the role of regulatory agencies.
- Alternatives to antibiotics?
- Links between basic and clinical research.
- Developing better diagnostics.
- Mechanisms and incentives to promote engagement between academia and industry.
- Facilitating best practice, such as data sharing and standardisation of methodology.

Conclusion

As expected, the discussion sessions raised far more questions than they answered. We hope that these questions will be a starting point for new research involving collaborations forged during these workshops, for example 65% of survey respondents connected with a potential research collaborator at the workshops.

We hope that participants will have been buoyed by funding announcements by the Cross-Council Initiative on AMR and inspired by experiences on the day of their workshop. Sustained funding and investment in interdisciplinary and pioneering basic research will be critical in tackling this global challenge.

LeSPAR would like to echo the closing remarks made by each of the workshop chairs by thanking all those involved in what was, we think, a successful series of workshops. We hope that this series of

workshops has facilitated the development of ideas and collaborations across the AMR research community.