Opportunities for where novel research in EPSRC remit can contribute to the multidisciplinary AMR challenge

By working in partnership across traditional discipline boundaries there is potential to create a step change in our understanding of resistant bacteria, their treatment and how to prevent spread. Opportunities exist across the breadth of EPSRC's remit for novel research that will address different aspects of the multidisciplinary AMR challenge. These areas are summarised below in no particular order:

1. **Novel diagnostics**

   A key factor driving the development of AMR is the lack of rapid diagnostic and disease surveillance technologies to detect early-stage infections in community settings. The result is that worldwide many infections remain undiagnosed or are diagnosed at a late stage. This leads to on-going transmission by people unaware of their infections and widespread inappropriate use of antibiotics which fuels drug-resistance. Late diagnosis also limits our ability to respond to emerging AMR strains. The development of the next generation of innovative point of care diagnostics is one of the highest priorities for improving the stewardship of current and future antibiotics.

   Early detection plays a crucial role in all treatment and prevention strategies. However, current gold-standard diagnostic tests (e.g. RT-PCR and bacterial culture) are slow and require samples to be sent to specialist laboratories. This leads to inherent delays between tests, results and clinical interventions. Public health intervention may be further delayed by a time lag of 1-2 weeks, associated with retrospective surveillance of laboratory tests.

   There are national and international drivers to widen access to rapid tests at the point-of-care (PoC) but current tests (*e.g.* lateral flow tests) are typically not sensitive to early infections, leading to missed opportunities for interventions.

   A new generation of innovative point of care diagnostics with data linkage is needed for community settings, including better antigen/antibody tests, molecular tests and tests which overcome the need to culture bacteria in order to test for antimicrobial susceptibility. These will be built on deeper understanding of the resistant bacteria and advances in next generation sensing technologies. The challenge is to integrate promising advances in underpinning engineering and physical sciences into simple hand held devices which can be used reliably in clinical and environmental settings. Such advances include new biomarker identification (including data mining for biomarker discovery), novel nanostars and quantum dots, microfluidics, miniaturised sensor systems, low power microelectronics and telecommunications. This requires partnership between industry and academia, and offers great opportunity to the private sector with are a number of companies (including small/medium sized enterprises) operating in this field.

   Rapid point of care diagnostics will play an equally important role in improving the stewardship of antibiotics, thereby preserving the effectiveness and reducing the risk of resistance.

   Diagnostics will also be needed to target any new non-drug based treatments that can avoid resistance.

There are major scientific and technological challenges associated with deploying new sensing technologies in community settings such as GP surgeries, care homes and pharmacies.

2. **Improved drug delivery strategies for antimicrobials**
Improved drug delivery strategies for small molecule antibiotics require an understanding of the physiological barriers to successful delivery and modelling the behaviour of nanoscopic materials in living systems.

A further key area of investigation would be the development of new strategies for administering antibiotics in a more targeted fashion to maximise the dose to infected cells whilst minimising systemic exposure and thereby the development of resistance. These could include chemical/biomedical engineering/new material approaches, engineering controlled release formulations targeted to specific tissues and the exploitation of device and drug combinations such as photodynamic therapy, ultrasound mediated delivery etc. All of these could be combined with new formulations of antibiotics and/or new vectors. This could also enable "near miss" shelved compounds to be utilised in the light of deeper analysis of the bacterial cell system.

3. **Novel synthetic approaches and innovative manufacture and scale up of new drugs and vaccines**
The development of new antimicrobial agents is needed as more and more strains of bacteria become resistant to current antibiotics. New, efficient synthetic approaches to identify and synthesise new classes of compounds that show antimicrobial activity are required. Traditionally, the process of moving from drug discovery to manufacture at scale is time consuming and research into the scale up and manufacture of novel antimicrobials and vaccines, will be key to accelerating the translation of new therapies in partnership with private companies. Natural product and biosynthetic chemistry strategies are opening up synthetic routes for laboratory production of novel antimicrobial compounds found in nature. Synthetic biology is also a potential route for the manufacture of phage treatments as an alternative to small molecule antibiotics.

4. **Smart surfaces and dressings to prevent infection**
New strategies to prevent infection are a major priority. Infection can be transmitted via surfaces, interfaces and materials (including those within medical devices, dressings etc.) which come into contact with humans, animals and the environment. The development of antibacterial surfaces and surface coatings for use in healthcare settings could reduce the risk of infection. Opportunities exist for frontier research at the interface between chemical sciences, advanced materials, engineering sciences, modelling, pharmaceutical sciences, life sciences and clinical science.

Research challenges could include for example novel surface chemistry for the development of antimicrobial surfaces- surface functionalisation and modification, surface characterisation and surface patterning at the nanoscale. These in turn would feed into work on interacting adaptive dynamic systems and externally triggered systems (such as responsive surfaces which deliver a response when required).

5. **Minimally invasive surgical techniques**

   A route to infection prevention is based on minimally invasive surgical procedures which could reduce the risk of infection by reducing the opportunity for exposure to infectious bacteria. The future trend is towards high precision and minimally or non-invasive approaches. Techniques such as robot-assisted surgery, image-guided interventions, smart instrumentation, augmented reality and laser surgery are already in clinical practice with future research leading to breakthroughs in areas such as robotic surgery and smart, targeted therapies; for example utilising biomaterials, nanomaterials or synthetic antibodies as delivery systems.

6. **Surveillance technologies and data analytics**

   As testing becomes more widespread there is a need for data linkage into clinical and surveillance pathways to prevent the spread of infectious diseases. This requires data analytics, innovative tracking technologies, mathematical modelling.

   Early detection capabilities could be improved by the use of web information and crowd sourcing to track infectious diseases across populations. Every week millions of people use the internet to search for information about health and self-report symptoms of an illness, often before they visit a doctor. For example, symptoms such as "fever", "cough" or "diarrhoea" are investigated using search engines (e.g. Google or Bing), and posted on social networking and microblogging sites (e.g. Twitter). Although not everyone who types in symptoms is actually ill, a pattern emerges from trends in the total number of anonymised searches and tweets.

   Up-to-date estimates of outbreaks based on web-information linked to current epidemiological information may enable doctors to better respond to AMR. Web-information also has the advantage that it could potentially track infections across a much larger proportion of the population than current surveillance and might identify outbreaks even before people attend clinics.

   The low cost of these methods is likely to be of particular benefit in resource-limited settings such as developing countries, where infectious diseases are an enormous problem.

   More research is needed to improve the evidence-base of these potentially highly valuable technologies and extend their use to AMR. Future research should target tools to improve their accuracy, geographical granularity and evaluate of their cost-effectiveness. However, one of the key challenges facing the academic community in this area is restricted access to data, such as queries and tweets, held by private companies. New public-private partnerships, policy changes, governance frameworks are urgently required to responsibly develop this powerful resource for AMR, balancing the privacy of individuals with the benefits of research for the public good. Data linkage to current surveillance systems will also be crucial.

7. **Water treatment technologies**

   The natural environment hugely influences the transmission of resistant bacteria and their genes at local and broad scales. Water quality especially plays a key role: i.e., poor water quality combined with the inappropriate use of antibiotics particularly in developing countries has been shown to lead to significant development and transmission of AMR. Therefore, much greater investment is needed to help improve sanitation and water quality in the emerging and developing world where a huge portion of serious multi-resistance develops. By funding

research to solve such problems, we will benefit the UK by reducing the probability of multi-resistance migrating to the UK, but also develop a deeper understanding of relationships between AMR, and waste and wastewater treatment applications within the UK itself. This includes understanding underlying molecular genetics and ecological principles related to transmission, but also diagnostic evaluations required to design and optimise treatment processes needed to reduce AMR bacteria and genes from any system. To deploy innovative diagnostics in such real world settings they need to be robust, specific, sensitive and simple to use with the capability for real time data connectivity and continuous monitoring.

8. **Tools for understanding bacteriology**

There are still gaps in our understanding of bacterial function. This includes how bacteria develop and transmit resistance, how they interact within their host environments and how their genomes control function. Deeper understanding of resistant bacteria will unveil new paradigms for diagnostics and surveillance and greater understanding of fundamental mechanisms of resistance development.

Systems biology and computer modelling approaches are needed in partnership with basic and clinical bacteriology to develop in silico models that can then be used to accelerate translation of potential treatment candidates. Solid state NMR, synchrotron radiation, neutron scattering and advanced imaging techniques can be used to provide a better understanding of bacteria and antimicrobial molecules and the molecular mechanisms of antibiotics at the single cell and single molecule level.