AMR policy dialogue: driving innovative solutions for antimicrobial discovery

Antimicrobial resistance (AMR) is a global strategic priority and sits within the UK Government's National Risk Register. By 2050, AMR is predicted to cause 10 million deaths, more than cancer. In 2019 alone, there were an estimated 4.95 million deaths associated with bacterial AMR.

Although global pharmaceutical research and development (R&D) spend continues to increase year on year, research into antimicrobial drug discovery is not currently an attractive commercial investment. This has had two major consequences: an ongoing decline of human capital for R&D in this field, and a decline over the longer term in availability of therapeutically effective antibiotics and other antimicrobial agents.

Concerted and coordinated efforts are needed to translate high-level policy commitments into strategic actions for long-term funding and support for the R&D of new antimicrobials.

Key messages

- The UK's human, infrastructural, and financial resource capacity is currently insufficient and inefficiently organised to effectively tackle AMR.
- New collaborative, integrative, and inter-disciplinary science discovery platforms are required, with tailored public/private models, which build upon recent investment, to help engage and train the next generation of research leaders and to incentivise and push products through the pipeline.
- Experience from Covid-19 can inform strategy and practice for antibiotic development by improving available clinical data and creating new mechanisms for collaboration and knowledge sharing.
- Increasing cross-sectoral coordination and expanding international collaboration, including with countries such as China to meet specific global patient needs, will drive appropriately targeted and well validated antimicrobial innovation and control of AMR.
- A 'call to action' by key stakeholders is urgently required to refocus political attention, emphasise the need for high-level leadership with cross-party ownership, and to clearly articulate what is required to fix current deficits in the UK's innovation system.

Introduction

On 16–17 May 2022, 22 stakeholders from UK initiatives, institutions, and funders concerned with strengthening collaboration and progress on AMR participated in a science-policy dialogue to discuss and give impetus to an action-orientated agenda for antimicrobial drug discovery.

The dialogue had three objectives:

1. To consider the implications of insights from prepared evidence briefings on the UK system for antimicrobial innovation and international partnerships for training and discovery.
2. To begin to construct a shared vision for a new approach to antimicrobial R&D.
3. To translate this vision into clear areas for action, collaboration, and coordination amongst dialogue participants and others.

This report synthesises the roundtable discussions around several themes and attempts to draw-out recommendations for action.

Human resources, training, and infrastructure

Human resource capacity for developing new antimicrobials is facing a significant challenge: as many large pharmaceutical firms have reduced their R&D in the antimicrobial space over the last 20 years, and as poor market and academic incentives fail to attract new people to replace those leaving the field, there are concerns that the community of expertise is shrinking in the UK. Associated infrastructures and networks have not been sustained. The field is characterised by often disconnected pockets of expertise located in universities and clinical settings, and in industry where the pipeline of R&D projects is widely understood to be insufficient.

Without longer-term funding delivered in a more coordinated fashion, there are fears that scientists will continue to be lost from the area. Assets resulting from research projects regularly become stranded in the academic lab as translational funding and support is insufficient to move them forward: many scientists have already pivoted to different therapeutic areas to safeguard career progression. Moreover, natural attrition of senior academic scientists will seriously deplete the availability of expertise, draining the academic pipeline of skills, knowledge, and wider institutional memory.

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Training and retaining scientists are clear priorities. Universities and funders need to provide sustainable funding to allow labs to develop long-term projects and centres that will attract PhD students, and early career fellowships, which are currently in short supply, to retain the best to take up post-doctoral positions and allow them to transition into independent leadership roles. Academic-industry partnerships and doctoral training centres can reinvigorate private-public links, expand skills, deconstruct sectoral silos, and build translation and commercialisation into research.

There are good examples of multidisciplinary doctoral training across UKRI doctoral training centres, for example, the AMR focussed **MRF DTP** that built PhD training across disciplines to align with the UK-wide research hubs. We have a moment in time now to build upon that multi-million pound investment and support these students to become future leaders in the field before they are lost to other careers, as their mentors will be close to retirement.

Reimagining how infrastructure is used within the community is necessary. Diamond Light Source is the single biggest science investment in the UK, and as part of the INSTRUCT-ERIC distributed research infrastructure, is a good example of a large, inter-disciplinary, integrative technology hub. It provides state-of-the-art resources, knowledge, and training. It is also flexible enough at short notice to play a lead role in the design and identification of anti-viral drugs to tackle the likes of SARS-CoV-2. However, development of, and access to, ‘plug-and-play’ technologies and networks requires strategic vision and incentives for researchers to focus on collaboration and problem-driven science. This is required to overcome traditional university

incentive and reward structures that hinder this type of work by emphasising prestigious publications above other objectives.

Rebuilding the antimicrobial community around new collaborative, integrative, inter-disciplinary platforms that can easily pivot to tackle a wide range of drug-resistant infections (bacterial, fungal and viral) is vital, especially within contemporary geopolitical contexts and new emerging infections. Senior figures who command influence and have significant resource-pulling capacity could work together to build pathways toward this. Crucially, this approach can draw in industry too, helping to connect R&D stages, improve communication and collaboration, and enhance coordination. Senior experts and industry leaders could work to co-create a new model to overcome identified barriers in new antibiotic development.

The talent pipeline for expert clinical microbiology and pharmacology is relatively fragile, hindered by a combination of a weakening academic base drawing new talent in, and roles becoming less attractive and less available. Experts with clinical experience point to the need to better bridge and combine skills from academic settings and across frontline roles to build capacity to manage AMR in clinical settings.

Solving these deep and long-term human resource, training and infrastructure challenges needs a new coordinated strategy. Reflecting on how the SARS-CoV-2 experience drove adaptations in scientific discovery, management, collaboration and coordination will be important. A post-pandemic UK-wide human resource study is required to update initial work done by the O'Neill Review. This would provide clear evidence to underpin new policies to strengthen the ecosystem.

Funding coordination and leadership

Research funding must be coupled with coordination, targeted to achieve both programmatical and infrastructural goals. Programmatically, facilitating an increase in research projects and activity across the spectrum of basic science, drug discovery, translational activities, and pre-clinical research, is crucial. This should provide opportunities for more people to enter the field and may lead to a diversity of new projects and the potential to carry them through the pipeline.

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Funding is also needed to help reshape AMR research infrastructure. Investment in capacity and capability is required to build long-term stability into the system. Organisations such as the Medicines Discovery Catapult are vehicles designed to help input to the knowledge base, linking technical expertise required to help academic-industrial translational work and bridge between key stages in discovery and development. Building clear pathways for progressing products with a patient-led focus is a priority.

As new antimicrobials can take 15 years to develop and reach the market, the lack of continuity and weak sense of coherence in the funding available over time is especially problematic. Since private funding such as venture capital is difficult to obtain for antibiotic drug development, efficient use of public and philanthropic funding becomes more important, especially in the short-term.

Funding earmarked for AMR as part of a focused UKRI strategic priorities funding programme could well serve this requirement. UKRI and other funding bodies have had experience of coordinating large funds and multidisciplinary teams (for example through the 'Tackling AMR – a cross council initiative' programme), however this has dropped off and it was indicated that momentum and coherence have dissipated in recent years.

Funding coordination and priority setting requires leadership. Dame Sally Davies, in her role as Chief Medical Officer (CMO), and Lord Jim O'Neill, are widely accepted to have provided strategic leadership and direction within the political mandate established by the then Prime Minister David Cameron. Dame Sally Davies was appointed as the UK's Special Envoy on AMR in June 2019, however this role is international facing. There was a broad consensus that there has been no clear replacement for the leadership provided by Davies and O'Neill, while the SARS-CoV-2 pandemic has reduced the political mandate for prioritisation that was cultivated under Cameron's premiership. As such, it seems there is a vacuum in strategic leadership around AMR in the UK.

It is unclear where ultimate responsibility should sit for driving forward innovation in new therapeutics to tackle AMR (be that an individual such as the CMO, a unit in the Department of Health and Social Care, or a new body). Crucially, the political mandate that supports leadership requires continuity through election cycles. AMR must find a new champion to ensure it regains relevance in the post-pandemic context, benefiting from, and interlocking with adjacent issues, rather than standing alone. These would encompass broader pandemic preparedness, diagnostics, and resilient health systems. Concrete steps need to be taken by senior figures in industry, academia, and public health to build a new coalition that can promote the need to identify and install the appropriate type of leadership.

Antibiotic usage and healthcare

The UK's surveillance and reporting of infection has supported stewardship efforts, providing annual targets and comparative data. Metrics and indicators must continue to be developed to ensure reporting mechanisms are robust during times of severe health system stress, such as during SARS-CoV-2.

Surveillance data also provides signals to the innovation system. Identifying targets and relaying those through funders to set clear, long-term priorities needs continued work. While lists, such as those for drug-bug combinations and priority pathogens do exist (issued by, for example, the World Health Organization and the English Surveillance Programme for Antimicrobial Utilisation and Resistance), a deeper 'steer' right through the system is needed. Analysis from January 2022 suggested that of the 22 UK-headquartered firms with pipeline projects, only 13 were developing products that matched listed priority targets.

Reporting and surveillance also connect with concerns about patient safety in hospitals. That the healthcare system itself is a threat vector is often overlooked: in the UK, one fifth of prescriptions are issued for infections that have been caught in healthcare settings, with these locations being "a reservoir of resistance." The paucity and fragmentation of AMR mortality data needs addressing.

The cost of antibiotics in frontline prescribing is a delicate balance of ensuring the price permits them to be used when required, while not encouraging overuse. Appropriate pricing of antibiotics is key to being able to use them at the hospital level while adhering to WHO 'Access-Watch-Reserve' (AWaRe) indexing and other

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stewardship principles. Clinical use settings need to be better supported as end-users and as sources of significant data that can feed back to direct the R&D ecosystem. Capacity to flexibly evaluate novel anti-infectives and treatment durations for various clinical indications through, for example, adaptive platform trials, would be of benefit. The success of such an approach has been highlighted by the UK's RECOVERY trial in identifying appropriate treatments for SARS-CoV-2.

In comparison to other areas of medical research, AMR has little charity or NGO representation: AMR impacts across many disease areas, making it harder to attract the focused charity representation that other disease areas benefit from. Societal discourse around AMR therefore requires development, that also may include enfolding AMR within the wider 'drug resistant infections' dialogue. This captures a broader range of microorganisms urgently requiring new therapies where the effectiveness of current drugs is being eroded due to the emergence of resistance. At least three interlocking efforts are required: capturing and listening to the patients' voices; working with charities in other disease/therapeutic areas to highlight the role of antibiotics in specific treatments; and expanding and augmenting data availability from clinical settings to demonstrate, in real-time, the threat posed by the emergence of resistance. Looking to efforts within the cystic fibrosis community, in particular work through the **CF AMR Syndicate**, may provide examples of good practice in relation to capturing and addressing patient need.

The state, private industry, and the antibiotic market

Despite global demand, the market for antibiotics is broken. The comparatively low price-per-dose, combined with the increased need for stewardship, limits the return on investment for industry. This has led to the collapse of even those companies successfully bringing new antibiotics to market. The bankruptcy of three US firms, Achaogen, Melinta, and Tetraphase, and the recently agreed shareholder purchase of Entasis, exemplify this.

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Configuring public/private involvement in this field is challenging. Uncertainty remains high regarding how investment should be raised, used, and repaid. While different perspectives exist on the relative ability of either the public or private sector to address AMR, a case was made for public sector investment in infrastructure, combined with a long-term, strategic research focus and support for new business models. Transforming how intellectual property and patents function within the antibiotic space is one potential focus for further attention.

Fresh thinking is required to change industry calculations to support antimicrobial innovation. An example of this is to reconceive antibiotics as a key part of the 'infrastructure of care' on the premise that a wide range of diseases often rely on antibiotics to treat infections that follow treatment. These infections often emerge as a result of the patient's immune system being compromised due to the primary illness, treatment (such as chemotherapy or surgery), or age. Antibiotics are, therefore, part of the infrastructure upon which modern medicine depends and without which more expensive, and highly profitable pharmaceutical drugs, would be ineffective. From this perspective, pharmaceutical firms should support antibiotic development as declining efficacy makes their more profitable products less effective and potentially renders these stranded assets. In the long-term, shareholder value is at risk if profitable products are susceptible to collapse due to a decline in the infrastructure of antibiotic cover for treatments that leave patients vulnerable to infection.

There is a reasonable understanding of the revenue companies need to allow antimicrobials to be an attractive investment. On that premise, the UK is trialling a delinked subscription payment model to purchase two existing antibiotics, Pfizer's ceftazidime-avibactam (Zavifecta) and Shinogi's cefiderocol (Fetcroja). It is recognised that the impact of the new model will only convince investors if other countries create similar incentive schemes. While the promise of the PASTEUR Act in the US is seen to be important, other countries globally will need to combine their approaches in order to re-shape the market at scale. In the long-term, success of the UK's new subscription model could result in a cascade of new schemes internationally that collectively reinvigorate pull incentives. The role of UK diplomacy will be important in realising this goal.

International collaborations and China

AMR is a global challenge requiring deep and sustained international collaboration to understand resistance patterns across geographies. International collaboration also provides important mechanisms for knowledge and infrastructure sharing; for developing new skills and building new teams; and for sharing costs and investment opportunities.

The SARS-CoV-2 pandemic demonstrated the necessity, and fragility, of global manufacturing and supply chains. Research and investment to collaborate on strengthening key logistics and infrastructures to deliver antimicrobials globally requires renewed focus. Importantly, the pandemic also shone a light on the value of scientific peer-to-peer communication and data sharing to accelerate therapeutic developments. It also highlighted the need to strengthen international collaboration in high priority long-term scientific efforts.

The increasing role of China as a centre of scientific R&D raises important new policy challenges. Close collaboration with China on AMR has been a UK strategic priority and it should continue to be so. Its history of pro-active industrial policy has resulted in significant growth in its biotech/pharmaceutical sectors, building a formidable research and manufacturing capacity. As AMR poses a significant threat to China's health security, research collaborations coupled with approaches to bring its industrial capabilities to bear in the global

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response should be of high priority for both the Chinese government and the international community.

However, contemporary geopolitical contexts and worsening bilateral relations hinder these efforts. The securitisation of infectious diseases such as SARS-CoV-2 and increasing technological rivalry with the US and other countries, raises the prospect of AMR being framed as a national security concern, with scientific data becoming less accessible and collaboration in 'sensitive sciences' being blocked.

Mutual mistrust and rivalry, along with efforts by Europe, the US, and others, to push back on broader Chinese influence threaten to exacerbate the situation. Therefore, health diplomacy efforts by a range of stakeholders will be of value to temper escalatory pressures. Finding creative ways to collaborate and continue dialogue are crucial. Connecting with the Chinese venture capitalist community may provide a new approach to leverage support for scientific collaboration. Other networks and previous research collaborations could also be revisited to try to maintain and build on informal connections to support knowledge sharing.

Additionally, using other frameworks can help to shore up diplomatic and expert connectivity to prevent communication closure. Such spaces can be crafted in reference to the UN Sustainable Development Goals, or under the auspices of the WHO or the Biological Weapons Convention, of which the latter two may provide forums for knowledge sharing and confidence-building.

A call to action

Given these issues and opportunities, a 'call to action', supported by a coaltion of leading experts from across sectors, is needed to clearly set out the challenges and propose options for making progress in therapeutic innovation to tackle AMR.

This can be a signal to government, demonstrating the unity of stakeholders and the significance of the issue. It can also present to funders and other research-supporting bodies the priorities that need to be addressed. Finally, it can help build public awareness through associated media coverage and wider advocacy.

Building on the considerable work undertaken over recent years to bring attention to the threat of AMR, now is the time to articulate what is required for the UK to mobilise its academic and industrial power to better tackle AMR. This should include:

- New flexible funding models to enable discovery projects access to national infrastructure and to support coordinated discovery activity across complementary specialist regional centres of excellence.
- Multidisciplinary junior- and early career postdoctoral AMR fellowships with 'on-the-job' training and discovery. This would build cohorts across academia and industry with skills and access to infrastructure in translational and fundamental science needed for challenge-led discovery.
- A focus to pursue the establishment of global partnerships to extend this approach and deliver national and regional solutions that contribute to the Sustainable Development Goals.

Key references

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