Innovate UK
KTN

Global Expert Mission
Antimicrobial Resistance US 2022

Contents

Abbreviations

ABR	Antibiotic Resistance
AMR	Antimicrobial Resistance
AMS	Antimicrobial Stewardship
AR Lab Network	Antibiotic Resistance Laboratory Network
ASF	African Swine Fever
ASP	Antimicrobial Stewardship Project
AST	Antibiotic Susceptibility Testing
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Innovation Organization
CARB	Task Force for Combating Antibiotic-Resistant Bacteria
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Center for Disease Control and Prevention
CIDRAP	Center for Infectious Disease Research and Policy
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DIT	Department for International Trade
EMA	European Medicines Agency
FDA	Food and Drug Administration
GP	General Practitioner
HHS	Department of Health and Human Services
IP	Intellectual Property
LMIC	Low- and Middle-Income Countries
MHRA	Medicines and Healthcare products Regulatory Agency
NARMS	National Antimicrobial Resistance Surveillance System
NCBI	National Center for Biotechnology Information
NDARO	National Database of Antibiotic-Resistant Organisms
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institute of Health
OGA	HHS Office of Global Affairs

Abbreviations

PASTEUR Act	Pioneering Antimicrobial Subscriptions To End Up surging Resistance Act (2021)
PATRIC	Pathosystems Resource Integration Center
PCVs	Porcine Circovirus Diseases
PERS	Personal Emergency Response System
POC	Point of Care
PRRS	Porcine Respiratory & Reproductive Syndrome
RTI	Respiratory Tract Infection
SIN	UK Science and Innovation Network
SME	Small and Medium-sized Enterprises
STI	Sexually Transmitted Infection
TB	Tuberculosis
USDA	United States Department of Agriculture
USAID	United States Agency for International Development
VMD	Veterinary Medicines Directorate
WHO	World Health Organisation

Welcome

As innovation is increasingly a global endeavour and the ambition of UK businesses to become truly international enterprises is at its highest, Innovate UK established its Global Expert Missions (GEM) Programme in 2017. Delivered by Innovate UK KTN in partnership with the UK Science and Innovation Network (SIN) and Department of International Trade (DIT), the GEM help further Innovate UK's global strategy by providing the evidence base for where it should invest and by providing the opportunities for UK businesses to build partnerships and collaborations with key economies.

Antimicrobial resistance (AMR) is one of the biggest threats to global health and food security today. The improvident use of antibiotics in both clinical use and animal husbandry has increased the prevalence of AMR. A systematic study on the global burden of AMR found almost 5 million deaths in 2019 were associated with AMR. This highlights the gravity of the situation and the urgency for international cooperation to mitigate the impact of AMR, which has been termed the "hidden pandemic".

The complexity of AMR owed to the intricate interrelationship between human and animal health, agriculture and the environment makes it difficult to tackle the problem through a single solution. It requires a holistic view through the One Health lens where all sectors work together in a coordinated approach to deliver solutions to combat AMR. The main strategies include:

1. Improved prevention of infectious diseases in humans and animals, including through improved hygiene and vaccination.
2. Improved and controlled use of antibiotics and other antimicrobials in humans, animals and agriculture ("stewardship").
3. Development and use of new antibiotics and other antimicrobials for human and animal use in a One Medicine approach.
4. Development and use of improved (rapid, affordable, reliable, point-of-care/pen-side) microbial diagnostics for human and animal use in a One Medicine approach.
5. Developing alternatives to antibiotics such as phage therapy for human and animal use in a One Medicine approach.
6. Preventing the discharge of antibiotics into wastewater and reducing/removing antibiotics already present.

The One Health approach draws relevant stakeholders together to co-create solutions. This mission explored opportunities for cooperation between the UK and the US on three thematic areas i) diagnostics, ii) therapeutics and vaccines, and iii) environmental surveillance. The UK delegates had the opportunity to meet with industry, policy, government and academic thought leaders to discuss opportunities and challenges in AMR and identified synergies between the two countries. The discussion largely focused on how the UK and US can develop long-term engagement through policy and R&D alignment to ensure innovative products and services are developed across the One Health landscape.

The US has provided significant financial contribution to developing new therapeutics and, with a strong research infrastructure, is well placed to bring innovations to the market. This was evident from our engagement with the Biomedical Advanced Research and Development Authority (BARDA) and Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), where they have a portfolio of 44 active projects and a network of four accelerators, one located in the US. Both organisations have a comprehensive programme where they provide access to funding for businesses seeking to develop new products and services in the US. There is an opportunity here to involve innovative UK-based businesses to utilise the expertise provided by BARDA. The Center for Disease Control and Prevention's National Antimicrobial Resistance Monitoring System provides surveillance data on enteric bacteria found in people, retail meat and food animals. While the US has a comprehensive R&D pipeline focusing on developing new therapeutics, there have been notable differences in approaching stewardship and One Health. It was clear that the UK is ahead of the US in stewardship and implementing a One Health approach in AMR policies. There was an observable difference in policy and behaviour regarding antibiotic use in the farming and agricultural industry. For example, in the US, the EPA has permitted the use of antibiotics across citrus groves to combat citrus greening caused by bacterial infection. To stimulate antibiotic development and provide economic incentives, the UK has launched the world's first subscription-based model for antibiotics. This is analogous to the PASTEUR Act which has not been approved yet by Congress. Although the US is behind the UK in AMR stewardship there is, however, a clear benefit for both countries to work collaboratively on stewardship, research and innovation.

AMR's challenges also provide commercial and collaboration opportunities for UK and US businesses. There is a clear need for novel therapeutic interventions including the development of new and improved vaccines, antimicrobials, and investment in novel phage technologies and microbiome-based therapies. Working towards a One Health approach means developing new therapies for human and animal use (One Medicine approach). Critical to AMR stewardship is the need for faster and more accurate microbial diagnostics and environmental monitoring. The report highlights key organisations in the US working to address AMR and the importance of working across multiple disciplines, such as human, animal, agriculture and the environment.

1. Introduction

Innovate UK's Global Expert Missions (GEM) Programme is pivotal in building strategic partnerships with countries and overseas organisations. It is an important tool to support the UK government's ambition and to be the international partner of choice for research and innovation. The GEM programme provides a deep dive into the research and innovation ecosystem in selected countries to help identify opportunities for UK innovation and shape future programmes by i) informing UK businesses and government, ii) Identifying innovation opportunities and building international collaborations, iii) promoting and sharing UK capabilities.

In September 2022, Innovate UK KTN took a team of UK experts representing businesses and academia to the US to improve Innovate UK's understanding of the research and innovation landscape in AMR in the US. The GEM explored potential collaboration opportunities in three thematic areas:
1.Diagnostics.
2.Therapeutics and vaccines.
3.Environmental surveillance.

Mission Objectives

AMR is a global challenge and is of strategic importance to the UK. The GEM is designed to identify international collaboration opportunities to support UK-based businesses. The objectives of the visit were:

1. Informing UK businesses and government

The findings and opinions of experts on the topic of the GEMs are made available to UK businesses and government departments. These inform UK businesses about potential opportunities for innovation in the country and the UK government on how it can help UK businesses make the most of those opportunities.

2. Building international collaborations

The expert insights will help inform how Innovate UK can best help UK businesses find and exploit the opportunities for innovation partnerships. The GEM creates connections with key organisations and people that will deepen and widen the collaboration with the partner country to benefit UK business.

3. Showcase UK capabilities

The GEM provides an opportunity to promote the UK's technological and business strengths to be the "partner of choice" in future innovation partnerships with strategic global economies.

1.1 Antimicrobial Resistance

AMR occurs when bacteria, viruses, fungi and parasites build up resistance over time after being exposed to antibiotics, antifungals or antivirals. This results in medicine that was once used to treat the infection becoming ineffective. Consequently, routine surgical interventions that was once safe can lead to serious and potentially fatal infections.

A recent study has shown that between 39% and 51% of bacteria which cause surgical site infection are already resistant to prophylactic antibiotics.[1] It is estimated that deaths due to infections that are resistant to antimicrobials will reach 10 million annually by 2050[2] with a cumulative Gross Domestic Product (GDP) loss of $100 trillion[3]. Undoubtedly global coordinated action is required to ensure sustained social and economic development. There is a concern that rising AMR will negatively impact the UN sustainable development goals (UN SDGs) which include no poverty, zero hunger, good health and wellbeing and gender equality. In a high-AMR impact scenario it is estimated an additional 24 million people will be forced into extreme poverty by 2030.

1.2 AMR in 10 Statements

AMR is a complex, multifaceted societal and economic challenge similar to other global challenges like climate change. In short, AMR can be described in 10 statements:

1. AMR is a global challenge affecting all countries and potentially impacting everybody; young and old, healthy and diseased. As a result of increased mobility, AMR has the potential to spread quickly around the globe.
2. AMR is often referred to as the hidden pandemic and is underestimated as a threat to health security. Currently it is not easy to diagnose and treat even if the causing microorganism has been identified and its antibiotic resistance profile determined. Furthermore, patient data may not always be documented and communicated to the relevant health authorities; there is no standardised system for recording the prevalence of AMR deaths.
3. Reducing antimicrobials for human and veterinary use is urgently needed and adds to the prevention of AMR. However, antimicrobials remain necessary; in countries where antibiotics are difficult to obtain and/or unaffordable, the chances of epidemics substantially increase[4].
4. AMR prevents the effective treatment of infectious diseases but also complicates medical treatments where antibiotics are used on a routine basis, such as surgery, chemotherapy and stem cell therapy.
5. AMR includes resistant bacteria but also viruses, fungi, yeasts and parasites. Recent outbreaks of resistant fungi (azole-resistant Aspergillus[5] and multidrug-resistant Candida[6]) show that these microorganisms increasingly threaten public health.
6. AMR so far has developed against all commercially available antibiotics. The emergence of resistant bacteria were found within months or years after and sometimes even before commercial introduction of antibiotics. The development of second and third-generation antimicrobial products were designed to target resistant microorganisms, however, some of these next generation antimicrobials are becoming ineffective.

7. The current pipeline of novel antibiotics is rather empty, despite the constant need for novel antimicrobial products and alternative strategies. Novel antibiotics are the most underserved area within drug discovery and development pipelines. The major reasons for this are the lack of economic incentives for companies to invest in a drug development pipeline for new antibiotics.
8. AMR at a global scale is escalating whereby low- and middle-income countries (LMICs) bear the harshest burdens in terms of fatalities, loss of livestock and economic losses. There are indications that climate change, especially observed in these LMICs, will further spread the impact of AMR.
9. AMR is considered a global One Health challenge involving both human health, animal health and the environment, together with related industries such as the agriculture and food (dairy, meat) sectors, the water sector and also the tourism sector.
10. There is no single solution to AMR. The impact of AMR can only be contained by coordinated efforts by international partners.

Key strategies to mitigate AMR

Both international and national level action plans have been set up to fight AMR by organisations such as the World Health Organisation (WHO), the Food and Agriculture Organisation (FAO), the European Commission (EC), the US Centre for Disease Control and Prevention (CDC) and others. These plans have five underlying strategies:

1. **Improving the prevention of infectious diseases** by raising awareness, improving hygiene and sanitation, and vaccination.
2. **Promoting antibiotics stewardship** by including the mandatory prescription of antimicrobials for human and veterinary use.
3. **Developing and applying improved microbiological diagnostics** for both microbial species identification as well as antimicrobial susceptibility testing.
4. **Developing new classes of antibiotics** and other antimicrobial products to which no resistance exists yet.
5. **Developing alternative antimicrobial strategies** that pave the way to entirely new therapeutic approaches to treat bacteria and other microorganisms, such as phage therapy, nanomaterials and microbiome-based therapies.

1.3 The UK National AMR Strategy and the Global Expert Mission

AMR is a serious threat to public health in the UK. NHS England's former Chief Medical Officer, Professor Dame Sally Davies, has reported that antibiotic resistance kills 5,000 people in the UK each year. This seems to be a conservative number and it is estimated at least 12,000 people in the UK are likely dying each year from drug-resistant sepsis alone[7]. In 2019, the UK government published its national action plan to tackle AMR. It set out a 20-year vision to combat AMR through:

1. Lowering the burden of infection and better treatment of resistant infections in order to effectively minimise the transmission of AMR across communities, including farming and food production communities, and the environment.
2. Optimal use of antimicrobials and good stewardship across all sectors, promoting access to safe and effective medicines that have been manufactured responsibly for all who need them.
3. New diagnostics, therapies, vaccines and interventions in use and a full AMR research and development pipeline for antimicrobials, alternatives, diagnostics, vaccines and infection prevention across all sectors.

The mission aims to complement the strategies proposed in the UK national action plan for AMR by working across business sectors and engaging with international partners. There is a focus on addressing these challenges through the One Health lens with an emphasis on human, animal and the environment. In particular, the mission addressed three key areas:

- **Diagnostics.** Conventional methods for bacterial diagnosis are tedious with high turnaround times often leading to empirical antimicrobial therapy and exacerbating the spread of AMR. There is an urgent need to develop rapid diagnostics tests for the identification and characterisation of resistant bacteria. Fast point-of-care diagnostics tests that can distinguish between viral and bacterial infection are critical in the healthcare process to significantly reduce antibiotic overprescribing.
- **Therapeutics including vaccines.** The development of new therapeutic interventions is vital to containing the spread of AMR. There has been a significant innovation gap in new antibiotic discovery, and since 1970 only a handful of antibiotics have been in clinical trial, with many being derivatives of known natural product antibiotics.[8] This, along with the economics of antibiotics has resulted in very few novel therapies succeeding in clinical trials. This GEM will aim to explore developments in new innovative therapies in human and animal interventions along with business models to support drug discovery.
- **Environmental surveillance.** Environmental monitoring of antibiotic usage and the prevalence of antibiotic resistance is key to mitigating the rapid rise of AMR. Surveillance has been recognised as a vital cog in the One Health approach to combating AMR. With a focus on water, soil and air, the GEM will focus on defining the objectives of AMR surveillance with a clear need to develop a harmonised international approach.

2. AMR in the US

AMR is an urgent global public health threat, causing at least 1.27 million deaths globally and associated with nearly 5 million deaths in 2019[9]. More than 2.8 million antimicrobial infections occur in the United States each year.

More than 35,000 people have died annually as a result, according to the Center for Disease Control and Prevention's (CDC) 2019 Antibiotic Resistance Threats Report[10]. When Clostridium difficile is included, the US toll for all threats in the report exceeds 3 million infections with a death toll exceeding 48,000. With the rise in AMR in the US, the Administration through the CDC has placed a number of measures to mitigate this. These include greater infection prevention and control, implementing policies to minimise antibiotic use and access, tracking data to monitor AMR outbreaks and investment in the development of new vaccines, therapeutics and diagnostics. It is clear that AMR is a pressing issue and concern for the United States with vast implications for public health. This has prompted a significant response from the government, industry and academia.

CDC watch list for emerging AMR threats in the US

There are a number of pathogens that are becoming increasingly resistant to existing antibiotics which is a growing concern for human and animal health. The CDC has been tracking several pathogens and has included them on the watchlist as potential threats that have the capability to spread rapidly. The most important resistant bacteria observed in the US include:

- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant Neisseria gonorrhoeae (N. gonorrhoeae)
- Multidrug-resistant Acinetobacter
- Multidrug-resistant Pseudomonas aeruginosa (P. aeruginosa)
- Drug-resistant Salmonella
- Drug-resistant Shigella

Other pathogens of concern:

- Clostridium difficile
- Drug-resistant Candida
- Drug-resistant Campylobacter
- Vancomycin-resistant Enterococcus (VRE)
- Methicillin-resistant Staphylococcus aureus (MRSA) and Vancomycin-resistant S. aureus (VRSA)
- Drug-resistant tuberculosis (TB)
- Drug-resistant Streptococcus pneumoniae
- Erythromycin-resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus

2.1 US AMR National Strategy

The latest US National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025[11], outlines coordinated and strategic actions to accelerate the US government's response to AMR. The strategy is based on the 2014 National Strategy for Combating Antibiotic-Resistant Bacteria and the first National Action Plan released in 2015.[13] Collectively, the documents have provided an evidence-based approach to strengthen policy, investment in R&D and expanding AMR surveillance and stewardship programmes. A key element of the renewed national action plan is the synchronisation of efforts in human, animal, agriculture and the environment.

The objectives of the national action plan are to:
- Slow the emergence and spread of resistant bacteria.
- Strengthen national health surveillance efforts to combat resistance.
- Advance the development and use of rapid and innovative diagnostic tests for the identification and characterisation of resistant bacteria.
- Accelerate fundamental and applied research for the development of new antibiotics, other therapeutics, and vaccines.
- Improve international collaboration and antimicrobial resistance for the prevention, monitoring, control and research and development of antibiotics.

In the period 2015-2020, the national action plan has led to the establishment of a network of research laboratories across the US with the aim of detecting, preventing, innovating and responding to emerging AMR threats.[14] In addition, it has helped launch a strategic initiative to support antibiotic stewardship in veterinary settings, the development of new programmes to improve antibiotic use across healthcare settings and the launch of the biopharmaceutical accelerator, CARB-X.

2.1.1 National Initiatives in the US to Combat AMR

The PASTEUR Act

The Pioneering Antimicrobial Subscriptions To End Up surging Resistance Act of 2021, or the PASTEUR Act[15] of 2021, was introduced in the House on 16 June 2021. The act authorises the Department of Health and Human Services (HHS) to contract much-needed antimicrobial drug subscriptions, which provides $11 billion in funding including other provisions. Antibacterial drug manufacturers approved by the Food and Drug Administration (FDA) can apply to HHS to list a drug as an urgently needed antimicrobial; the HHS will then review and sign a subscription agreement. Within six years of the bill's enactment, the Government Accountability Office will submit a study of the bill's effectiveness in developing priority antimicrobials to Congress. The bill has been introduced to the House but has not been passed.

Antimicrobial Resistance (AMR) Challenge

The CDC, together with the HHS Office of Global Affairs, led a year-long international effort that resulted in more than 350 organisations pledging to slow the impact of AMR on the world.[16] This challenge was launched and concluded at the 2018 and 2019 United Nations generals, respectively.

Antimicrobial Resistance (AMR) Diagnostics Challenge

The Antimicrobial Resistance (AMR) Diagnostics Challenge was a joint effort between the CDC, FDA, National Institutes of Health (NIH), and the Office of Assistant Secretary for Preparedness and Response/Biomedical Advanced Research and Development Authority (BARDA) to identify innovative and rapid diagnostic tests at the point of need. The final prize of $19 million was awarded in 2020 to Visby Medical, Inc for their device that detects the bacterium responsible for gonorrhoea and determines its sensitivity to ciprofloxacin in 30 minutes.

CDC and FDA Antibiotic Resistance Isolate Bank

The CDC and the US Food and Drug Administration (FDA) launched the Antibiotic Resistance Bank in 2015 and continued to expand and increase the diversity of resistant bacterial and fungal pathogens for research and development of new therapies.[17]

FDA Guidance for Industry

The FDA implemented the Guidance for Industry (GFI) #213 in 2017 after extensive collaboration with the animal industry, veterinary organisations, animal breeder organisations and the animal feed industry.[18] As a result, 100% of medically important antimicrobial drugs used in food or water of food-producing animals have either been withdrawn from the market or voluntarily changed from over-the-counter to veterinary supervision or prescription status. As a result, the policy has eliminated these products in food producing animals. The FDA and the United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service and National Veterinary Accreditation Program collaborated to develop a new veterinary feed directive module to educate veterinarians on these policies[19]. The impacts of veterinary feed directive are not yet known and will be measured in the coming years.

Genomics for Food Safety Consortium

The Genomics for Food Safety Consortium includes the FDA, CDC, USDA's Food and Inspection Service, Agricultural Research Service, APHIS NIH's National Library of Medicine (NLM), and the National Center for Biotechnology Information.[20] The consortium coordinates, strengthens and leads whole genome research efforts, focusing on priorities for molecular sequencing of foodborne diseases and zoonoses. The consortium then uses the information collected to support surveillance and outbreak investigations.

Global Health Security Agenda

Multiple US departments and agencies, including USAID, HHS Office of Global Affairs (OGA), CDC, State, and USDA work together through the Global Health Security Agenda (GHSA) AMR Action Package to strengthen national capacities to address antimicrobial resistance.[21] This includes multisectoral coordination, surveillance, infection prevention and control, and antimicrobial stewardship.

National Antimicrobial Resistance Monitoring System (NARMS)

NARMS, established in 1996 is the United States public health surveillance system that monitors antimicrobial susceptibility of certain enteric bacteria found in people, retail meats and foodstuffs.[22] NARMS is a collaborative programme between the CDC and state and local health departments, FDA and USDA. This national public health surveillance system tracks changes in antimicrobial susceptibility to certain gut bacteria found in humans (CDC), retail meat (FDA), and livestock (USDA) in the United States.

NCBI National Database of Antibiotic-Resistant Organisms (NDARO)

NDARO is a collaborative, interagency, researcher-accessible centre for AMR data to facilitate real-time monitoring of organisms.[23] The database contains genomic data for nearly every one of the pathogen isolates collected from publicly available information. As part of the 2015 plan, the NIH/NLM/NCBI partnered with several agencies, including the FDA, CDC, USDA, World Health Organisation (WHO), Public Health England, and others to take steps to maintain an organised database of antimicrobial resistance genes.

2.2 Overview of Leading Organisations in the US

CDC

The CDC is part of the Department of Health and Human Services' main operational divisions. It is responsible for preventing the transmission and introduction of infectious diseases as well as offering advice and support to other countries and international organisations to help them improve their disease prevention and control, environmental health, and health promotion initiatives.

The Antibiotic Resistant (AR) Investment Map[24] shows CDC's key activities in the US and abroad to combat antimicrobial resistance by investing in laboratory and epidemiological expertise plus public health innovation. CDC supports most of these activities through its AR Solutions programme, whilst leveraging investments in successful programmes across the agency for maximum efficiency.

The CDC plays an integral role in developing the WHO Global Antimicrobial Resistance Surveillance System (GLASS)[25] and the Emerging Antimicrobial Resistance Reporting (EAR) portal.

CARB-X

CARB-X finances the early development of antimicrobial agents, vaccines, and rapid diagnostics. It has a portfolio of 44 active CARB-X projects and 12 completed projects. It has established a network of four accelerators, one of which are in the US:

- Institute for Life Sciences Entrepreneurship (ILSE)[26]

In addition to funding, CARB-X also provides valuable services and expertise to a portfolio of therapeutics/vaccine and diagnostics companies. CARB-X is funded by BARDA, the Wellcome Trust in the UK, Germany's Federal Ministry of Education and Research, the UK government's Department of Health and Social Care (through its Global Antimicrobial Resistance Innovation Fund), the Bill & Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases.

BARDA

The Biomedical Advanced Research and Development Authority, or BARDA, funds the development of medical necessities such as vaccines, drugs and therapies, and plays a key role in implementing the federal government's national AMR strategy. They also create necessary diagnostic tools for chemical, radiological, nuclear, bacterial and viral health emergencies in accidents, attacks and pandemics. BARDA primarily focus on 21st-century health security threats as a reason to encourage the advanced development of medical countermeasures in conjunction with other private companies. By collaborating with the private sector through unique public-private partnerships, BARDA has become a leader in the production of antibacterial medical countermeasures. The goal of these partnerships is to spur scientific innovation, which can then be implemented by physicians to treat serious health threats like antibiotic-resistant bacterial infections. BARDA has assisted with the end-to-end development of antimicrobial products; from early research and licensure to commercialisation support. They provide capital and expertise to pharmaceutical companies working on novel antimicrobial drug candidates.

BARDA, alongside NIH-NIAD, covers therapeutics and diagnostics development in AMR but the caveat for BARDA funding and support is the need for projects to be linked to the bio-threats agenda. Through CARB-X, BARDA has moved to funding earlier stages, including pre-clinical. However, their primary focus remains the clinical stage and commercial development. BARDA are geography agnostic, and if the company meets their criteria, it will fund or guide companies to a more relevant funding scheme. The Division of Research, Innovation, and Ventures (DRIVE),[28] covers early-stage diagnostic development. Ventures[29] is another funding option from BARDA that works in a similar fashion to venture capital by taking equity and reinvesting it. Ventures has the same scope as BARDA and will also scout new technologies from regular funding calls as well as across the globe (e.g. through accelerators) to find those that align with BARDA's investment strategy. Figure 1 (on page 20) highlights the role and responsibility of BARDA and how it relates to other government departments in the development of therapeutic interventions for human use.

NIH-NIAID

The NIH-National Institute of Allergy and Infectious Diseases (NIH-NIAID) funds and conducts AMR-related research and supports the development of new, faster microbiology diagnostic tests. Its research programme also focuses on ways to prevent infection, including vaccines, and the development of new antibiotics and treatments that are effective against drug-resistant microorganisms including viruses, bacteria, parasites and fungi.

NIH-NIAID provides funding for non-traditional therapeutics including advancing research for live microbiome-based products, bacteriophages, and other novel treatment options. For example, NIH-NIAID has funded work on the development of mannosides, which instead of killing bacteria, prevent infection by stopping bacteria from binding to host tissues. In 2020, an NIH-supported mannoside product advanced to become part of the CARB-X portfolio. NIH-NIAID also supports research on the optimisation of dosing levels, duration, route of administration, and use of combination drug therapy to suppress the emergence of resistance and minimise toxicity.

ARAC

The Antibiotic Resistance Action Center (ARAC) was established to protect the efficacy of antibiotics through advocacy, research, and science-based policy. Experts in communications, policy, microbiology, epidemiology, and other fields make up ARAC, a group dedicated to developing novel approaches to tackle antibiotic resistance. Its primary goal is to unite scientists, medical professionals, communications specialists, and policy experts to work continuously to combat these superbugs and safeguard antibiotics. Their recommendation is “use as little as possible but as much as necessary”.

NIAMRRE

The National Institute of Antimicrobial Resistance Research and Education (NIAMRRE) promotes knowledge and education on the use of antibiotics, stewardship, and microbial resistance. With a One Health perspective, NIAMRRE works to advance the goals outlined in the US National Action Plan to Combat Antimicrobial Resistance. To tackle the global challenge of antimicrobial resistance in humans, animals, and the environment, NIAMRRE promotes cross-sector collaboration and coordinated action via:

- Establishing networks and resources to further AMR research.
- Increasing awareness of AMR and its stewardship through education and outreach.
- Bringing together AMR stakeholders from many sectors to take action.
- Increasing AMR awareness and promoting AMR-specific funding.

PACCARB

The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) is made up of federal and non-federal subject-matter experts in human and agricultural health.[30] The PACCARB informs the President on relevant initiatives and policies that will strengthen the HHS Secretary’s skills to prevent, diagnose, mitigate, or treat infections that are resistant to antibiotics.

CIDRAP

The Center for Infectious Disease Research and Policy (CIDRAP)[31] conducts research and converts scientific knowledge into useful, practical applications, policies, and solutions in order to prevent illness and death from specific infectious disease risks. It fulfils its mission through information synthesis, communication, consensus building, research, education, and training. Antimicrobial stewardship practice, research, and policy are all covered by the CIDRAP Antimicrobial Stewardship Project (ASP), which provides free, high-quality information and educational materials. It has a vibrant website created to actively engage a wide and global audience.

IDSA

With more than 12,000 members, the Infectious Diseases Society of America (IDSA)[32] is a network of specialists in infectious diseases in medicine, science, and public health. Its mission is to promote excellence in patient treatment, education, research, public health, and infectious disease prevention with the goal of enhancing the health of individuals, communities, and society.

CC4CARB

The NIH-NIAID is the principal organisation behind the Chemistry Center for Combating Antibiotic Resistant Bacteria (CC4CARB).[33] The aim of the centre is the synthesis and dissemination of a rationally designed chemical library that can be used in drug development. CC4CARB helps to speed up drug discovery and development process targeting Gram-negative bacteria.

CDDEP

The independent, multidisciplinary research conducted by the Center for Disease Dynamics, Economics & Policy (CDDEP) aims to improve the health and welfare of humans globally. CDDEP was established with a focus on leveraging research to assist in improving health policy decisions. Research on malaria, antibiotic resistance, disease control priorities, environmental health, alcohol and tobacco, and other global health challenges is conducted by CDDEP experts using a variety of disciplines, including economics, epidemiology, disease modelling, risk analysis, and statistics. Africa, Asia, and North America are all included in the worldwide scope of CDDEP initiatives, which include scientific research and policy engagement.

The CDDEP team has expertise in dealing with regional and national problems as well as local and international facets of problems like antibiotic resistance. Innovative design and analysis methods are a hallmark of CDDEP research, which is extensively disseminated through conferences, papers, and web-based tools. Projects of CDDEP include:

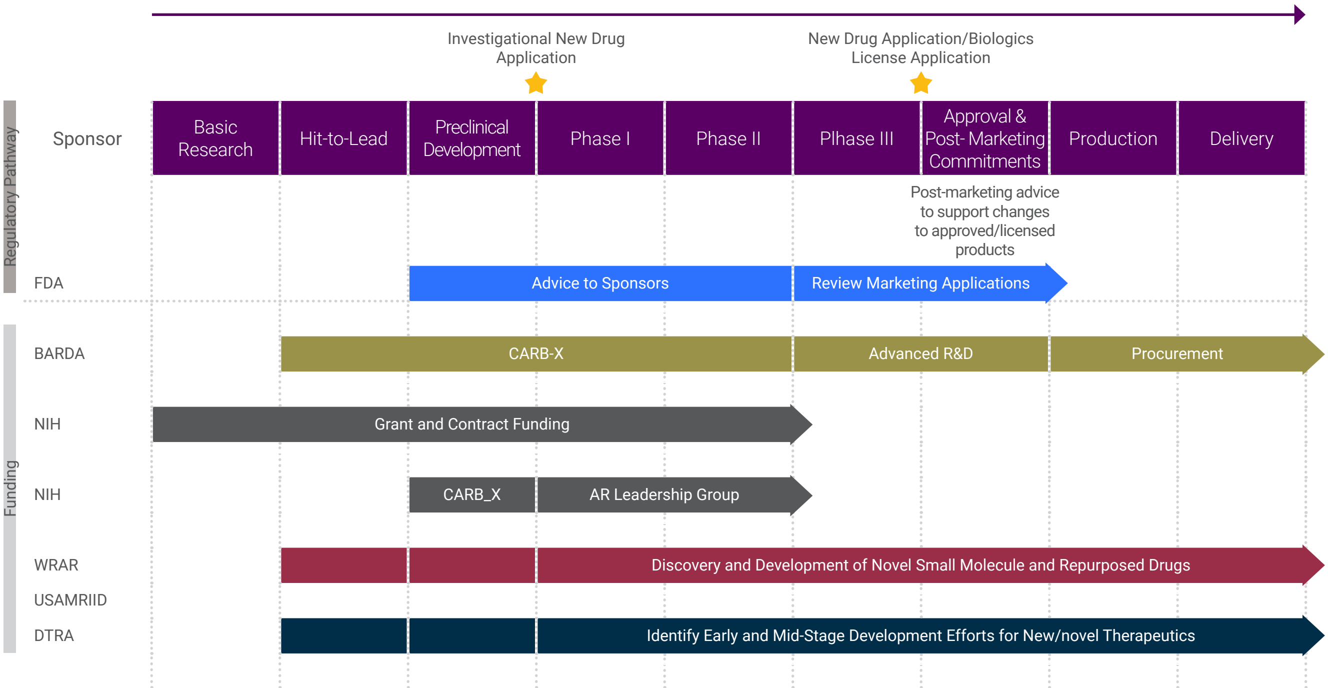
- Resistance Map: Launched in 2010, this is an interactive set of graphs and maps that displays global statistics on antimicrobial use and resistance at the national and subnational levels.[34]
- Mapping Antimicrobial Resistance and Antimicrobial Use Partnership (MAAP): The Fleming Fund Regional Grant Program in Africa is being carried out by several partners from Africa.[35] The study aims to collect retrospective data on AMR and antibiotic use from public and private institutions through Africa.
- Regulatory landscape for AMR: The goal of the landscape analysis is to shed light on the current R&D environment for antibiotics and the regulatory perspectives surrounding the introduction of novel antibiotics in South Africa, Brazil, and India.

In October 2022, the One Health Trust (founded as CDDEP) officially launched.

BIO

The world's largest advocacy organisation, the Biotechnology Innovation Organization (BIO), comprises member firms, state biotechnology organisations, academic and research institutions, and other associated organisations from all over the US and more than 30 other countries. Members of BIO work on the creation of cutting-edge biotechnology products for the environment, agriculture, and healthcare. Additionally, BIO organises the BIO International Convention, the largest gathering of the biotechnology industry in the world, as well as important investor and partnership gatherings that take place all around the world. BIO One-on-One Partnering, arguably the industry's top partnering software, organises 50,000 in-person meetings annually between investors, biotechs, pharmaceutical firms, academic institutions, and non-profit organisations at live events.

Human drug approval process



Animal drug approval process

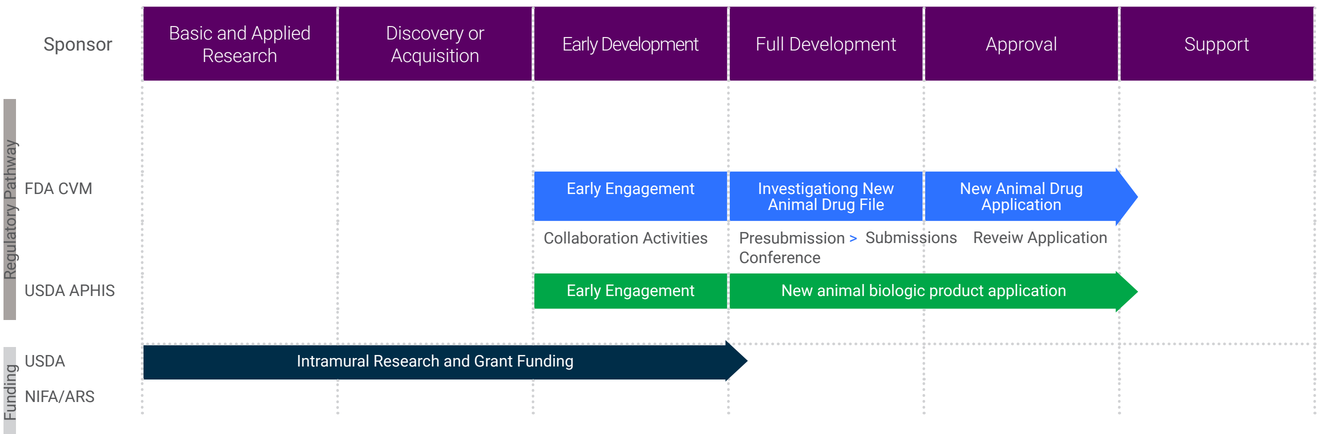


Figure 1. Federal agencies involved in the R&D pathway and regulatory approval for human drugs. Source: Figure has been adapted from the National Action Plan for Antibiotic-Resistant Bacteria Year 5 Report.[36] WRAIR: Walter Reed Army Institute of Research, USAAMRIID: The United States Army Medical Research Institute of Infectious Diseases, DTRA: Defense Threat Reduction Agency.

2.3 US Businesses Working in AMR R&D

The US hosts a wide range of companies (Figure 2 on page 25) relevant to the three thematic areas of the mission:
- Diagnostics.
- Therapeutics and vaccines.
- Surveillance and monitoring of AMR in the environment.

2.3.1 Diagnostics

In the development of microbial diagnostics, a distinction is made between microbial identification and antibiotic susceptibility testing (AST). The application of both can contribute to the reduction of antimicrobial resistance. Ultimately, there is a need for fast, reliable and affordable, point-of-care (POC) tests for both identification as well as AST.

The providers of innovative microbial diagnostics in the US is dominated by large multinational companies such as BD, Cepheid, Roche Diagnostics, bioMerieux and ThermoFisher. These companies have significant market share and capabilities to scale operations globally. Recently there has been a number of smaller diagnostic companies that have emerged with new and innovative technologies that are disrupting this market. However, due to the challenging market dynamics for diagnostic devices, these smaller companies often find it difficult to raise significant capital and acquire meaningful market share.

CARB-X plays a critical role in funding global antibacterial innovation with a focus on early-stage research. Table 1 provides a list of diagnostics companies that are funded by CARB-X.

Table 1: Selected CARB-X-funded AMR diagnostics companies in the US

Accellerate Diagnostics	Novel optical imaging technology aims to rapidly identify infectious microbes to help clinicians speed the treatment of patients with sepsis or at risk of sepsis.
Avails Medical	Electronic antibiotic susceptibility test (AST) using electronic biosensors.
Baebies	Small footprint diagnostic instrument for rapid diagnosis of neonatal sepsis.
DayZeroDiagnostics	Proprietary machine-learning algorithm analyses the genomic data to identify the pathogen and determine its antibiotic susceptibility.
Pattern Biosciences	Rapid identification and antimicrobial susceptibility test (ID/AST) to diagnose drug resistant infections.

2.3.2 Therapeutics and Vaccines

The suppliers of innovative (and generic) antibiotics in the US consist of large multinational companies such as Johnson & Johnson, Merck, Pfizer, Abbott and Viatris. These organisations develop new antimicrobial agents and vaccines as well as producing and marketing their own products. There has been rapid innovation and developments in vaccine technology for human health and with companies increasingly viewing One Health as the key driver, these will eventually filter into animal health.

In addition, the US has several small and highly innovative companies that are developing new antimicrobial products and vaccines. Due to the economic climate and the poor return on investment it is becoming increasingly difficult for smaller companies to secure investment for R&D. Fortunately, there are a number of "push" and "pull" mechanisms to fix what is referred to as the "broken antimicrobials market". CARB-X has a portfolio of SMEs that it has funded in recent years with Table 2 highlighting a selection of SMEs funded by CARB-X in new therapeutics development.

Table 2: Selected CARB-X-funded AMR therapeutics and vaccine companies in the US

Affinivax	Vaccine Staphylococcus Aureaus (SA) using the Multiple Antigen Presenting System (MAPS) vaccine technology platform.
Amicrobe	Large molecule therapeutic design for direct application to tissues.
Cellis Therapeutics	Nanosponge project using the natural receptors on human macrophage membranes.
Clarametyx Biosciences	Monoclonal antibody designed to rapidly collapse bacterial biofilms.
Entasis Therapeutics	Direct-acting small molecule therapeutic targeting the penicillin-binding proteins.
Forge Therapeutics	Novel therapeutics targeting metalloenzymes.
Integrated Biotherapeutics	Novel vaccine consisting of five components representing toxoids for seven SA toxins.
Locus Biosciences	Precision medicine utilising the natural lytic activity of the bacteriophage along with the DNA- targeting activity of CRISPR-Cas3.
Lumen Biosciences	Oral antibiotic-alternative biologic cocktail developed with Lumen's proprietary manufacturing process that utilises spirulina expression.
Microbiotix	Bacterial trans-translation inhibitors into a new class antibiotic for use as a single-dose oral therapy to treat sexually transmitted infections caused by multidrug-resistant Ng.
Peptilogics	Engineered peptide-based antibiotics to address difficult-to-treat infections.
Summit Therapeutics	Novel class of antibiotics with a new mechanism of action that acts via the bacterial target, LolCDE.
Trellis Bioscience	Native human monoclonal antibody, disrupting bacterial biofilm by extracting a key scaffolding protein.
Vaxcyte	Innovative vaccine to prevent pharyngitis (Strep Throat).
Vedanta biosciences	Live therapeutic, new treatment modality with a broad-spectrum of activity.
Venatorx	Oral cyclic-boronate penicillin-binding proteins inhibitor for 3rd-generation-cephalosporin (3GC)-resistant gonorrhoea.

2.3.3 Surveillance and Monitoring of AMR in the Environment

Environmental monitoring is vital to controlling and managing AMR. From a One Health perspective, surveillance is critical to monitor usage, outbreaks and preventing leakages into the environment. With the daily use of antibiotics in humans, animals and the agri-food sector, it is almost inevitable that these agents will end up in the environment via:

- Wastewater from manufacturing, ordinary households, nursing homes and hospitals.
- Farms, animal shelters and veterinary clinics.
- Use of antimicrobial agents in agriculture for crop protection.

AMR surveillance is currently conducted at the federal level through the NARMS project managed by the CDC. However, there are opportunities for companies to develop new and improved tools for surveillance and environmental monitoring.

Antibiotic use in agriculture: Streptomycin to prevent citrus greening

Citrus greening also known as huanglongbing (HLB) is a bacterial disease primarily affecting citrus trees. First reported in China in the mid-1900s, it eventually reached Florida leading to a 80% decline in citrus production.[i] Overall, the disease has resulted in 72% decline in the production of oranges in the US in the last decade.[ii] In 2021, the EPA announced the use of streptomycin which has shown to suppress HLB disease to mitigate the spread of citrus greening in Florida.[iii] With concerns around AMR in the environment and agriculture, the USDA/NIFA announced an investment of $5 million to mitigate AMR across food chain.[iv] The University of Florida will study the effects of antibiotic use on naturally occurring bacteria and characterise development of AMR.

i. Agrilife Today: New research takes aim at devastating citrus greening
ii. Chemical and Engineering News: Citrus greening is killing the world's orange trees. Scientists are racing to help
iii. EPA Takes Aggressive Actions Against Citrus Greening While Maintaining Public Health and Environmental Protections
iv. USDA NIFA Invests More Than $5M in Mitigating Antimicrobial Resistance Across the Food Chain

Figure 2. Geographic location of AMR stakeholders in the US

3 Research and Innovation Opportunities

Research and innovation, including the three thematic areas of the mission, is critical to developing tools, technologies to monitor, diagnose, treat and prevent AMR in human, animal and the environment. This is a global challenge affecting both low- and middle-income countries (LMIC) and high-income countries (HIC). There is a need for global cooperation to co-create innovative products, services and solutions.

The GEM team had the opportunity to engage with key stakeholders working in the AMR field to better understand the challenges and opportunities in developing new diagnostics and therapies for AMR. There was a particular focus on understanding the US AMR market and the research and innovation landscape to identify areas where UK businesses can contribute and benefit. There is a clear drive by the Administration to invest and develop market-leading technologies to curb the rise of AMR, which was evident from the visit. The mission identified a number of opportunities for developing innovative products and services across the three thematic areas.

3.1 Diagnostics

AMR diagnostics spans the areas of human and veterinary diagnostics as well as the detection of resistant pathogens and genes (including antimicrobials) in the environment. While the One Health approach brings these disciplines together, there are subtle differences in quality, test and reimbursement systems in diagnostics.

Overall, the diagnostics market is highly fragmented for both human and veterinary applications. There are many commercially available tests (based on different technologies) for both human and veterinary applications. This means that the exchange of information is very limited. Each diagnostic system developed is unique and has a different characterisation profile (i.e. time taken for results, sensitivity). Providers often remain with a diagnostic system they are accustomed to and unlikely to switch. Without a standardised system for collecting and sharing diagnostic data across human and veterinary health, it leads to the development of diagnostics based on vastly different technologies, which leads to market saturation.

While there are a number of new test systems under development, the vast majority of these will struggle to reach the market due to the high cost of market entry and poor return on investment. Therefore, it is common for smaller diagnostics companies to focus on early technology development followed by a standard exit strategy to sell the technology to larger diagnostics companies such as Roche, bioMerieux and Lab Corp. However, there is a caveat that these established diagnostics companies are seeking technology that can i) improve and extend their line of products, ii) provide faster and more reliable testing, and iii) fits within the company's operation and processes.

Challenges and opportunities in diagnostics for AMR in human and animal health

The development of affordable and rapid POC tests is critical to managing and controlling the spread of AMR. However, a number of challenges need to be addressed for the diagnostics market to flourish. Currently, there is no economic incentive for clinicians/general practitioners to carry out a diagnostic test, whereas there is an economic uplift for prescribing medicine. The reimbursement model makes it difficult to justify diagnostics tests that take >15 min for a result. There needs to be a shift in the payer model to accommodate POC tests. As a result, there is a lack of investment and incentives to develop new diagnostics tools for AMR. Combined with poor regulatory alignment and lack of guidance on end-point, clinical trials have become more expensive and time-consuming. There is also a need to fast-track access to intellectual property (IP) at the academic level where it is common for universities to take a substantial share of a spin-out company, making it less attractive to venture capital funding.

In animal health, there is a lack of communication between authorities. Animal isolates and sequencing data are routinely collected but are not widely shared with industry and with the relative authorities. There is also a shortage of biobanks for animal isolates in the US which prevents industry from utilising and developing appropriate intervention and diagnostic tools for farm animals. In addition, there is a disconnect between veterinarians and farmers on the availability of diagnostics for animal health and monitoring. In response to this, the US has set up an excellent network of organisations that are working to raise awareness and educate on AMR and the importance of diagnostics.

Despite these challenges, there remains significant opportunities to invest and develop in new diagnostics for AMR.

- Development of rapid, affordable and accurate diagnostics for POC testing in primary and community care settings. Incentivise the use of diagnostics in the clinical setting to promote antibiotic stewardship.
- The utilisation of AI and digital solutions to analyse data and support healthcare professionals to triage and in the decision-making process. Digital technology to guide the patient journey and first- and second-line antibiotic use and treatment to minimise over-prescribing.
- Invest in the development of next-generation technologies, including CRISPR and graphene sensors.
- Genomic data sharing and better access to isolates to facilitate collaboration between diagnostic companies. Due to the highly competitive nature of the field there is a lack of knowledge exchange which needs to be overcome.
- Driving behaviour changes through education and awareness to increase the use of diagnostics in stewardship programmes and for the continuous learning and development of doctors and healthcare professionals.
- There needs to be a major re-think of the reimbursement model for AMR to facilitate the use of POC diagnostics in clinical settings.
- Improved access to diagnostics expertise at regional labs.
- Invest in developing viral and bacterial POC tests for farming. There are a few priority areas, including the detection of Salmonella in milk.

3.2 Therapeutics and Vaccines

The discovery and development of novel therapeutics for clinical adoption have been largely impeded by technical, regulatory and economic challenges. The investment required to develop new classes of antimicrobials poses too great of a risk for investors and pharmaceutical companies which is primarily driven by economic uncertainty. The poor ROI has led many companies to minimise investment or abandon R&D in antimicrobials. This void in antimicrobial development was filled by smaller, highly innovative companies seeking to exploit high-risk academic research for potential commercial returns. Companies globally are investigating innovative antibacterial therapies many of which are based in the US.

Market and technology challenges for developing new antimicrobials and therapies

Technology push and market pull mechanisms are being developed to give both large and smaller companies prospects for developing new antibiotics. Technology push mechanisms involve funding the development of new antibiotics. The market pull mechanisms are the attraction of commercialising newly developed antibiotics. An example of this is the UK's subscription model and the PASTEUR Act in the US. While these policies are a step in the right direction and given how quickly resistance can evolve, focusing on antibiotic development alone is not sufficient to address AMR. It is imperative that there is R&D investment in other technologies, including phage therapy, vaccines and microbiome intervention. All types of intervention will likely be needed to combat AMR effectively (see Figure 3), and while resistance can emerge for all therapies, it has been shown that there is a much lower probability of resistance emerging when using vaccines[37].

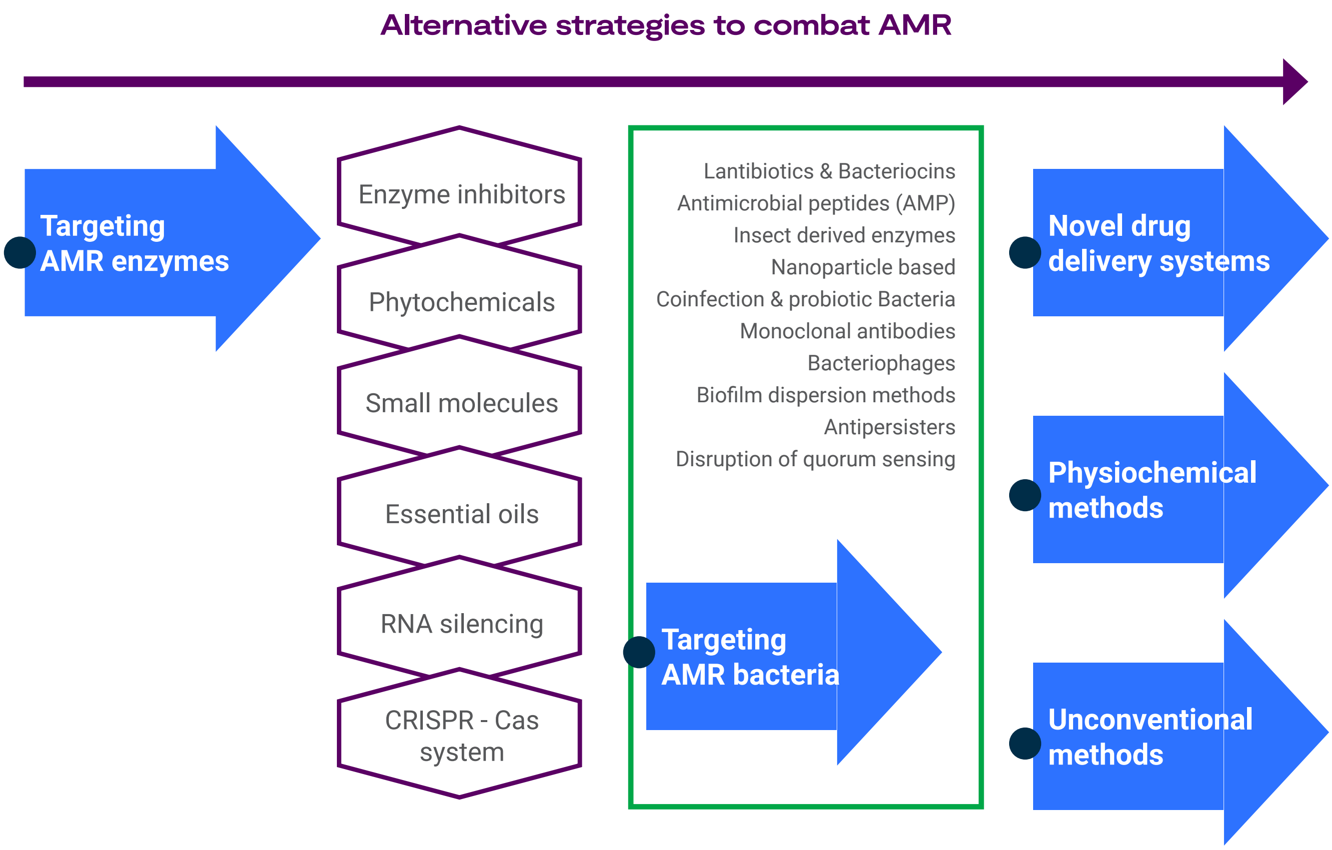


Figure 3: Schematic overview alternative strategies to combat AMR[38]

Similar to how bacteria can become resistant to antibiotics, fungi can also acquire resistance to antifungal medications, and this is a growing concern as very limited antifungals are available. This means resistance will drastically reduce the range of available treatments. Some fungus, including Candida auris, have the potential to develop resistance to every antifungal medication used to treat fungal infections. This is particularly concerning for patients that may suffer from invasive fungal infections—severe infections that involve the blood, heart, brain, eyes, or other areas of the body.

AMR in animal healthcare faces similar challenges. While the use of critically important antibiotics (CIAs; these antibiotics are critically important for human health) is limited in animal husbandry, there is much greater use of lower-risk antibiotics. This, however, is the opposite for companion animals such as cats and dogs, which are often treated with CIAs such as third or fourth generation cephalosporins and fluoroquinolones. These companion animals are much more likely to be in close physical proximity to human owners that may be immunosuppressed and therefore pose a much greater risk to the transfer of resistant microorganisms to the human population compared to farm animals.

While there are a number of fundamental challenges in developing novel antimicrobials, there is an opportunity to exploit new technology and our understanding of microbiology to develop novel therapies.

Vaccines

- Development of vaccines designed to be compatible for human and animal use. This would require companies developing human vaccines to allow animal health companies to license and develop the technology for animal use. This has not happened to date, as most companies simply do not extend their research and technology to animals. This will be a new framework for developing a vaccine for all under the One Health approach.
- Develop vaccines for common pathogens. Many companies do not have the expertise in vaccine development to combat AMR and the market for this therapy.
- Leverage mRNA vaccine platform to develop vaccines for bacterial pathogens. The “plug and play” model of the platform can potentially reduce R&D costs and time to vaccine development.
- Increase use and development of autogenous vaccines for animal healthcare.
- Develop RNA vaccine technology for veterinary use. For example, to treat Porcine Respiratory & Reproductive Syndrome (PRRS).
- Research on vaccine delivery/carrier systems that increase thermal stability without the need for cold chain to ensure improved vaccine deployment to remote areas in LMICs.
- Development of tools to better understand the role of cellular immune protection in vaccination programmes.
- Education for better prevention of cure.

Antimicrobials and alternative therapies

- Development of antibiotics and antimicrobials that are microbiome sparring for targeted drug delivery.
- Use of digital technologies such as telemedicine, triage and prescribing to prevent AMR spread.
- Development of phage therapy. There are a number of US companies developing this technology for human health. However, there are currently no guidelines for regulation and licencing.

- Development of microbiome-based therapies such intestinal microbiota transplants and live biotherapeutic products.[39]
- Development and understanding the mechanism of action of antimicrobial peptides as alternatives to antibiotics.
- Embrace gene editing, development of platform technologies and access to biobanks.

Phage technology to combat AMR

Bacteriophages (phages) are viruses that infect bacteria and have very precise targets. Phage therapy involves killing human disease-causing bacteria while leaving other bacteria unharmed by using active phages. Phage treatment offers promise as an alternative to antibiotics in the fight against existing and developing infectious illnesses and antimicrobial resistance. Due to the enormous biodiversity of phages in nature and the use of more sophisticated technology to identify them, the finding of new phages has increased recently. In contrast, the discovery of novel antibiotics has slowed.

3.3 Environmental Surveillance

Environmental monitoring is critical in the One Health approach to tackling AMR. The need to better understand the role of the environment in the spread of resistant bacteria is key to curbing the rise of AMR. Environmental monitoring ensures antimicrobials released into the environment through waterways and other sources are controlled and limited. Surveillance does not represent an industrial sector on its own. It covers both public and government as well as private and industrial organisations, including public and private laboratories, analytical and engineering companies. For the most part, surveillance of resistant organisms in the US, as in the UK, is based on the identification of particular strains following a clinical observation of a resistant infection. This retrospective approach can inform on the importance of infections but cannot predict future infections.

Surveillance tools and approaches that are used today

1. Organisations involved in monitoring environmental quality:
    a. Sampling and sample transport techniques.
    b. Antibiotics and other antimicrobials.
    c. Bacteria and other micro-organisms.
    d. Antibiotic resistance genes.

2. Organisations involved in the generation or treatment of waste, for example, wastewater treatment and the environment either in local (hospital-based) treatment units or centralised sewage/wastewater treatment plants, or air filtration from composting plants:
    a. Preventing the discharge of substances including antimicrobials or co-selective agents, resistant microorganisms or resistance genes.
    b. Reducing concentrations of antimicrobials and microorganisms by removal from wastewater and the environment.

3. Organisations offering related products and/or (consulting) services. It is important to capture and track AR data generated over time so that trends can be identified. Based on these trends, policies can be set or amended.

The UK and US are already working together on environmental monitoring, and several opportunities exist to strengthen this partnership.

- The use of big data and machine learning to develop algorithms to better predict disease outbreaks.
- Develop new monitoring strategies in animal husbandry. There is evidence that monitoring temperature, humidity, water intake by pigs, the density of pigs per square metre and using an AI model can help predict an outbreak of an infection within a couple of days allowing the farmer to act and revert the situation to avoid the outbreak.
- Develop on-site testing kits and sample preservation for faster sample analysis.
- Increased data sharing on antibiotic use in farms and AMR in the human population to monitor the rise and spread of resistant bacteria.

3.4 Antimicrobial Stewardship

Although not defined as a thematic area for the mission, discussions suggested that antimicrobial stewardship (AMS) in both human and animal healthcare is definitively a topic of interest.

The US is considered to be behind the UK in stewardship, particularly in veterinary health. However, there are opportunities for both the UK and the US to work together on this which needs to be driven by leaders in both the human and veterinary health professions. The feed additive regulations introduced in the US in 2018 is a fundamental step in the right direction which prohibits medication by farmers and antibiotic use which is now under the jurisdiction of the veterinarian. With some reports suggesting that this has not led to a significant reduction in the use of antibiotics, there is a need to understand why there has been little change and is vital to developing new stewardship programmes.

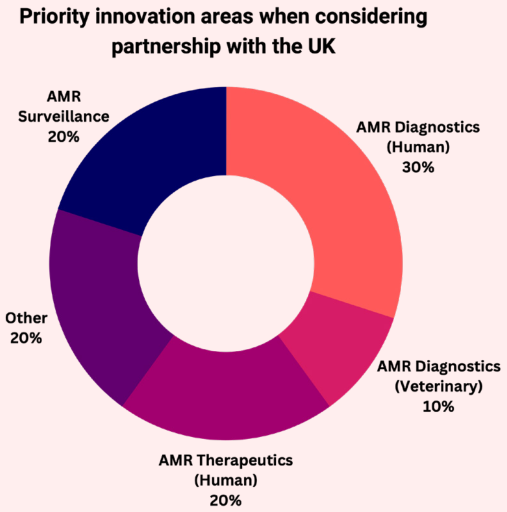
The medical system in the US favours a flat rate consultation for primary care which would include any diagnostic testing. This means there is no incentive for a primary care physician to undertake diagnostics before prescribing a drug (for which they would be paid), including antibiotics. Without a behavioural change in medical practitioners and a system that incentivises good practice, AMR will continue at pace.

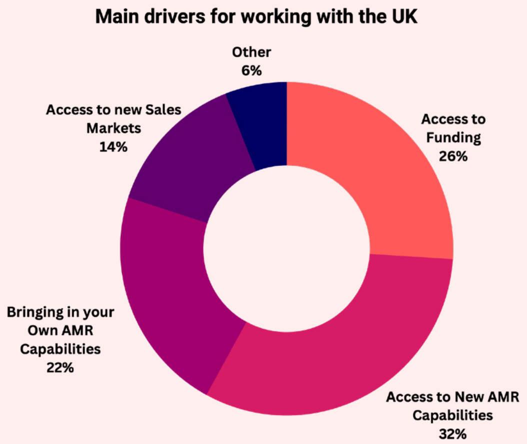
The UK One Health approach to antimicrobial stewardship is world-leading. This is illustrated in the recent United Nations Food and Agriculture Organisation (UN FAO)/UK Veterinary Medicines Directorate (VMD) report.[40] The GEM found that AMR stewardship could be improved in US primary care settings, and a need for wider public engagement of diagnostic testing, especially in primary care in the US. Overall, the US has made great progress in combating AMR, however, it seems rather siloed regarding AMR stewardship. Its socioeconomic model also appears to make it difficult to promulgate stewardship compared to the development and use of therapeutics.

UK Session at the World AMR Congress

The World AMR Congress provided an opportunity to network, share ideas and build an international partnership with leading minds in the field of AMR. A dedicated UK session in the conference programme enabled delegates to showcase capabilities in the UK and highlight synergies and opportunities for global cooperation. The discussion focused on diagnostics, therapeutics and vaccines and environmental surveillance in both human and animal health. In addition, the topic of One Health was introduced, leading to a discussion on AMR stewardship and the need to re-think how therapeutics are developed for both human and animal use. An interactive Q&A provided insights into the challenges and opportunities for UK-US collaboration in AMR. The data shown below was collected from the UK highlight session using Mentimeter.

Diagnostics for human health was the highest priority when considering innovation areas, followed by therapeutics and surveillance. With stewardship increasingly important in curbing the prevalence of AMR, diagnostics is critical to ensuring the appropriate use and management of antibiotics. A key driver to working with the UK is access to new capabilities, funding and investment, and the opportunity for US businesses to promote their capabilities.

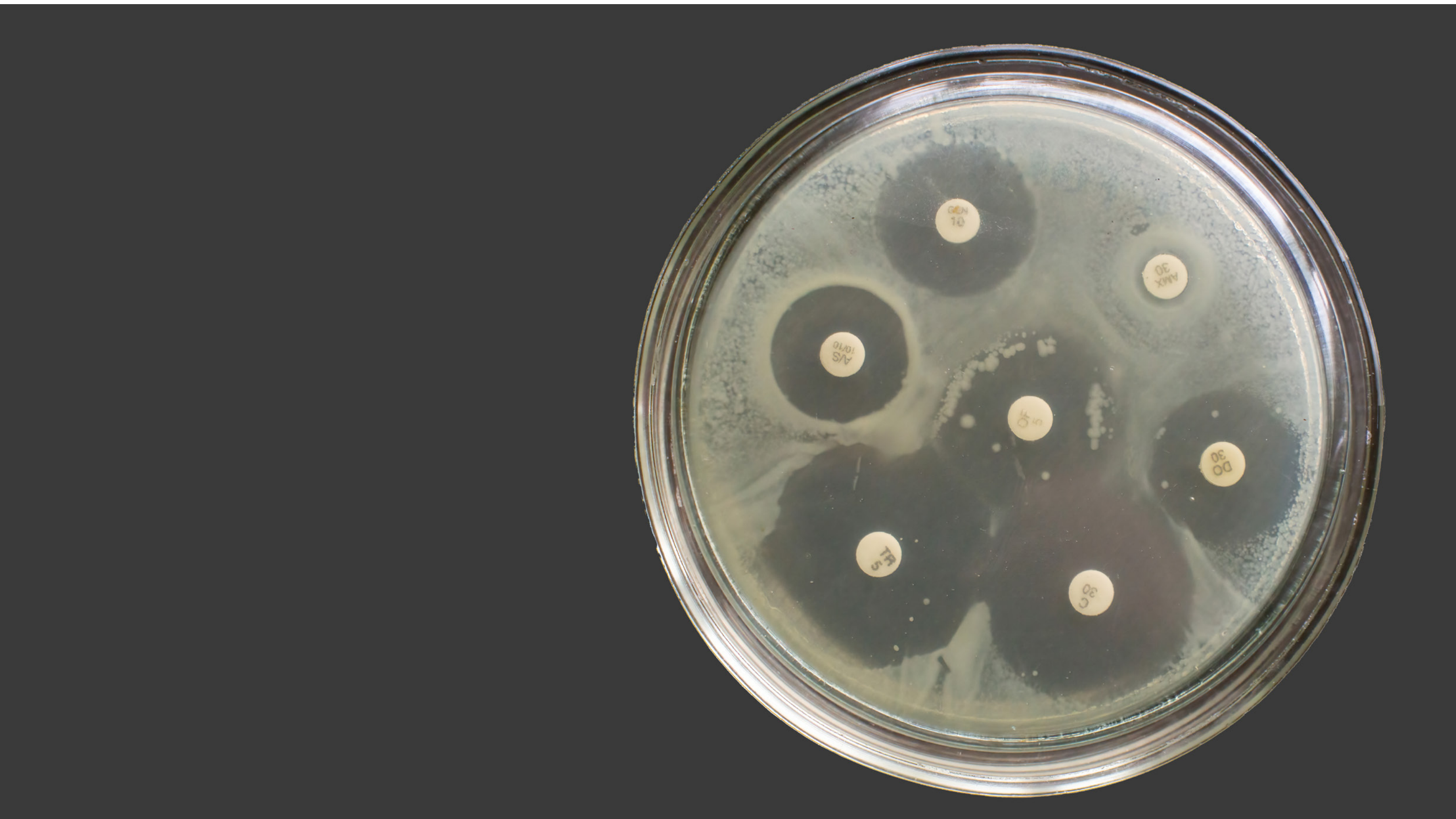




3.5 Conclusion

Antimicrobial resistance is a major threat to human health and has long been recognised as a hidden pandemic. AMR is not isolated to certain countries or regions, but its reach is global, impacting countries recognised as having excellent healthcare systems including the UK and US. While the impact of AMR may seem inevitable, there is a global movement and awakening to this hidden pandemic that offers hope and optimism. The UK and the US have set out national action plans with a clear vision to mitigate the impact of AMR. These include investment in new diagnostics and therapeutics, development of effective stewardship programmes and the need for global cooperation. In addition, a growing number of organisations are dedicated to policy, education and funding of research and innovation. For example, the $1 billion AMR Action Fund is one of the largest public-private partnerships dedicated to investing in the development of new antimicrobials.

The UK and the US are uniquely positioned to bring together various industrial sectors and disciplines to co-develop novel solutions to address the problems presented by AMR. These include the development and exploitation of platform technologies in the field of molecular biology, vaccinology and the microbiome. In addition, data-driven science will be a key enabler by leveraging AI and machine learning in bioinformatics to monitor AMR outbreaks. This mission has shown that there are a number of synergies and opportunities between the UK and the US to align policy and prioritise specific areas for R&D. The US provides plenty of opportunities for funding, including access to venture capital funds, a knowledge base and networking opportunities. Through the various government departments and organisations, the US is well positioned to deliver on their AMR National Action Plan. The UK has a number of highly innovative businesses and research institutes working towards the development of new diagnostics and therapeutics. In particular, the UK is strong in AMR stewardship, an area where the US can benefit. Overall, the mission successfully identified several areas for collaborative R&D and joint policy development that will provide social, environmental and economic benefits to the UK and the US.



Annex 1: Task Force for Combating Antibiotic-Resistant Bacteria (CARB)

The National Strategy is implemented by a Task Force for Combating Antibiotic-Resistant Bacteria (CARB). The Task Force published the first National Action Plan for CARB in March 2015 with the intention of guiding the country toward the National Strategy's goals by setting precise targets, policies, and benchmarks to be reached.

The Task Force for Combating Antibiotic-Resistant Bacteria includes:

- The Department of Health and Human Services (HHS) and its following components:
  - AHRQ - Agency for Healthcare Research and Quality
  - ASPE - Assistant Secretary for Planning and Evaluation
  - ASPR - Assistant Secretary for Preparedness and Response
  - BARDA - Biomedical Advanced Research and Development Authority within ASPR
  - CDC - Centers for Disease Control and Prevention
  - CMS - Centers for Medicare and Medicaid Services
  - FDA - Food and Drug Administration
  - NIH - National Institutes of Health
  - OGA - Office of Global Affairs

- The United States Department of Agriculture (USDA) and its following components:
  - APHIS - Animal and Plant Health Inspection Service
  - ARS - Agricultural Research Service
  - FAS - Foreign Agriculture Service
  - FSIS - Food Safety and Inspection Service
  - NIFA - National Institute of Food and Agriculture
  - OCS - Office of the Chief Scientist

- The Department of Defense (DoD) and its following components:
  - DHA - Defense Health Agency
  - GEIS - Global Emerging Infections Surveillance
  - IDCRP - Infectious Disease Clinical Research Program
  - MIDRP - Military Infectious Diseases Research Program
  - MRSN - Multidrug-Resistant Organism Repository and Surveillance Network
  - PVC - Pharmacovigilance Center
  - WRAIR - Walter Reed Army Institute of Research

- Department of the Interior (DoI)
- Department of State (DoS)
- Environmental Protection Agency (EPA)
- United States Agency for International Development (USID)
- Department of Veterans Affairs (VA)

Annex 2: Stakeholders with their URL

Authorities	
BARDA	https://aspr.hhs.gov/AboutASPR/ProgramOffices/BARDA/Pages/default.aspx
CDC	https://www.cdc.gov/
CSIS	https://www.csis.org/analysis/us-government-and-antimicrobial-resistance
Department of Health and Human Services	https://www.hhs.gov/about/agencies/oga/global-health-security/antimicrobial-resistance/index.html
FDA	https://www.fda.gov/
NIAID	https://www.niaid.nih.gov/
NIH	https://www.nih.gov/
US Department of Agriculture	https://www.usda.gov/topics/animals/one-health/antimicrobial-resistance-overview-amr
USAID	https://www.usaid.gov/global-health/health-systems-innovation/health-systems/combating-antimicrobial-resistance

Antibiotics and vaccines	
Abbott	https://www.abbott.com/
Affinivax	http://www.affinivax.com/
Amicrobe	https://www.amicrobe.com/
Cellix Therapeutics	http://www.cellics.com/
Clarametyx Biosciences	http://www.clarametyx.com/
Entasis Therapeutics	http://www.entasistx.com/
Forge Therapeutics	http://www.forgetherapeutics.com/
Integrated Biotherapeutics	http://www.integratedbiotherapeutics.com/
J&J	https://www.jnj.com/
Locus Biosciences	http://www.integratedbiotherapeutics.com/
Lumen Bioscience	http://www.lumen.bio/
Merck	https://www.merck.com/
Microbiotix	http://microbiotix.com/
Peptilogics	https://www.peptilogics.com/
Pfizer	https://www.pfizer.com/
Summit Therapeutics	https://www.summittxinc.com/
Trellis Bioscience	http://www.trellisbio.com/
Vaxcyte	https://vaxcyte.com/
Vedanta Biosciences	https://www.vedantabio.com/
Venatorx	http://venatorx.com/
Viatris	https://www.viatris.com/en

Diagnostics

Accellerate Diagnostics	https://acceleratediagnostics.com/
Avails Medical	http://www.availsmedical.com/
Baebies	http://www.baebies.com/
BD	https://www.bd.com/en-us
bioMerieux	https://www.biomerieux-usa.com/
Cepheid	https://www.cepheid.com/en
DayZeroDiagnostics	https://www.dayzerodiagnostics.com/
Pattern	https://www.pattern.bio/
Roche Diagnostics	https://diagnostics.roche.com/nl/en/home.html
ThermoFisher	https://www.thermofisher.com/nl/en/home.html

Funders

Bill & Melinda Gates Foundation	https://www.gatesfoundation.org/
CARB-X	https://carb-x.org/
PEW Trusts	https://www.pewtrusts.org/en/projects/antibiotic-resistance-project
World Bank	https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future

Other

American Society for Microbiology	https://asm.org/
AMR Resistance Fighter Coalition	https://antimicrobialresistancefighters.org/
Antimicrobials Working Group	https://antimicrobialsworkinggroup.org/
California Life Sciences Institute	https://www.califesciences.org/
CC4CARB	https://www.cc4carb-collection.org/
CDDEP	https://cddep.org/
CIDRAP	https://www.cidrap.umn.edu/
CSTE	https://www.cste.org/page/ARS
IDSA	https://www.idsociety.org/public-health/antimicrobial-resistance/antimicrobial-resistance/
ILSE Bio	https://ilsebio.com/
Iowa State AMR Consortium	https://www.amr.iastate.edu/
MassBio	https://www.massbio.org/
NIAMRRE	https://www.niamrre.org/
RTI International	https://www.rti.org/
UN	https://www.un.org/en/
Washington Center for One Health Research	https://deohs.washington.edu/cohr/antimicrobial-resistance-0
World Bank	https://www.worldbank.org/en/topic/health/brief/antimicrobial-resistance-amr

Annex 3: Meeting Report by Matthew Diasio, British Embassy Washington

Summary

Professor Dame Sally Davies, UK Special Envoy on Antimicrobial Resistance (AMR), visits Washington, DC, as part of a broad campaign to encourage US political and public action on AMR, including a new public diplomacy effort based on a unique musical theatre production about Sir Alexander Fleming. The Administration is increasingly vocal about its commitment to tackling AMR as a health and biodefense security issue, with clear opportunities to collaborate with the UK on the pandemic instrument, G7 innovation workstreams, and supply chain transparency.

Musical Diplomacy

1. The UK Science and Innovation Network (SIN) helped bring The Mould that Changed the World [https://www.mouldthatchangedtheworld.com/], a Scottish musical about Fleming's discovery of penicillin and early fears about AMR, to the US. The musical brings together arts and sciences to engage the public on AMR, featuring local healthcare workers and scientists in the chorus, and is supported by a schools programme of engagement for children. It had two sell-out runs at the Edinburgh Festival Fringe in 2018 and 2022, and toured UK schools to raise awareness about AMR and promote proper stewardship of antibiotics.
2. Through the work of SIN, Davies and DHSC, The Mould that Changed the World secured philanthropic and corporate sponsors in the US, including the Rockefeller and CDC Foundations, Merck, Cepheid, and the industry-led $1 billion AMR Action Fund. His Majesty's Government fundraising built on initial efforts by the British Society for Antimicrobial Chemotherapy (BSAC) - a well-renowned UK learned society.
3. As part of a public diplomacy campaign, figures in government, industry, academia, and media attended the Washington run of The Mould that Changed the World. The New York Times and Forbes both commended the musical for creatively raising awareness, and linked the musical with UK policy objectives on driving antibiotic innovation.
4. The cast also performed a curated selection of songs as part of the opening ceremonies for IDWeek, the largest gathering of infectious disease physicians in the US, along with remarks by Davies. In recognition of her leadership, the organisers have invited Davies to give keynote remarks at next year's conference.
5. The cast and chorus performed a short version to nurses, doctors, and patients at the Children's National Hospital, to much acclaim for the UK's innovative leadership by President and CEO, Kurt Newman.
6. The musical will continue its SIN-supported run in Atlanta from 1- 6 November.

Policy Engagement

7. Davies' visit provided an opportunity to engage the US system and multilaterals on AMR. Meetings with the Pan-American Health Organization and World Bank laid the groundwork for action leading up to the 2024 UN High-Level Meeting on AMR at the General Assembly in New York. Davies also offered to share policy papers with national breakdowns of the mortality burden of AMR that were developed by the GRAM (Global Research on Antimicrobial Resistance) project, partially funded by the DHSC Fleming Fund.

8. Davies was joined by the director of CARB-X, a public-private partnership to encourage innovation in combatting AMR, in giving a briefing to staff on the Senate Health Committee. Drawing on the latest data from GRAM, which showed that AMR already kills more people annually than HIV/AIDS or malaria, Davies stressed that AMR is an issue that needs to be confronted now. The CARB-X director emphasised modern medicine could not exist without antimicrobials. Davies also provided information on NHS England's new subscription model to financially incentivise research and development, of novel antimicrobials and to bring these essential medicines to market. This model formed the basis of joint commitments by G7 Health and Finance Ministers under the UK's Presidency and reiterated under Germany's Presidency, to strengthen antibiotic innovation.
9. In a session with Senate staffers, Davies heard how the PASTEUR Act, a bipartisan bill in both chambers of Congress based in part on the NHS model, is currently stalled in committee. The bill's sponsors hope it can be passed after the midterm elections, but it is unclear if the PASTEUR Act is likely to be included in must-pass legislation. They plan to share UK success stories to persuade more members of Congress to support it.
10. While Davies was in Washington, President Biden signed a national security memo on countering biological threats and released a new national biodefense strategy. The strategy builds on Biden's 2021 American Pandemic Preparedness Plan, which proposed manufacturing prototype vaccines for all pathogenic virus families, and includes AMR as a threat for the first time. The UK's G7 commitments on antimicrobial supply chain security align with this direction of travel.
11. In a meeting with the Office of Science and Technology Policy (OSTP), they announced they now have a staffer dedicated to AMR, reflecting their increased focus on the issue. Since Dame Sally's last visit in March, the US has become more forward-leaning on the pandemic instrument, and is now advocating for any accord to take a strong One Health approach. OSTP highlighted that provisions for national surveillance capacity are a priority, agreeing that systems should be able to pivot between AMR and pandemic outbreaks.

Comment

12. The musical provided an innovative basis to showcase UK leadership on AMR where there are positive signs of momentum in the US, including increased public awareness, political will and VC resources. USG and multilateral officials were particularly interested in the results of the UK-funded GRAM project while Senate staff were keen to understand G7 commitments to subscription-based financial incentives for antimicrobials that the UK secured.
13. Dame Sally's visit also revealed the scope for wider UK/US collaboration on biosecurity and life science capabilities. GCSA Sir Patrick Vallance's visit in early November will be an opportunity to progress this, including with ARPA-H, the US's new high-risk, high-reward biomedical research agency.
14. With misinformation and disinformation on health, a shared challenge faced by both the US and UK, building trust in communities through strong public health communication, and linking arts and sciences together, offers an opportunity for both countries to demonstrate leadership and ensure better preparedness for current and future health emergencies.

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38 Courtesy: Prof Jayaseelan Murugaiyan, Department of Biological Sciences, SRM University-AP, Guntur District, Mangalagiri 522240, Andhra Pradesh, India

39 An example of a product derived from donor samples includes SER-109 from Seres Therapeutics. SER-109 has reached phase III and targets C.difficile infections.

40 Tackling Antimicrobial Use and Resistance in Food-Producing Animals. Lessons Learned in the united Kingdom.

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