White Paper

Steps Towards Addressing Antimicrobial Resistance

The need for novel approaches to boost R&D pipelines

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Introduction

Antimicrobial resistance (AMR) continues to represent a substantial risk to healthcare provision and economic stability globally. In 2021 alone, 4.71 million deaths globally were associated with AMR bacteria, including 1.14 million attributable deaths.[1,2] Forecasts suggest that 8.22 million deaths associated with AMR could occur globally in 2050, but that 92.0 million deaths could be cumulatively prevented between 2025 and 2050 by better management of severe infections and improved access to antibiotics.[3] The World Bank estimates that AMR could lead to $1 trillion additional healthcare costs by 2050, and $1 trillion to $3.4 trillion in GDP losses per year by 2030.[4] There has been significant attention paid to AMR in 2024, with key global meetings focusing on the urgent need for action, including the need to stimulate clinical innovation. An effective response to AMR requires a concerted, cross-sector, global approach. Challenges and progress in the context of research and development (R&D) are described in this white paper.

COMMITMENTS FROM GLOBAL AMR MEETINGS IN 2024: WORLD HEALTH ASSEMBLY

Antimicrobial resistance: Accelerating global and national responses[6] (May 27 – June 1, 2024; Geneva, Switzerland)

- Delegates approved a resolution to accelerate global and national responses to AMR
- Report highlights inadequate R&D pipeline for new antimicrobials
- Strategic priorities identified as including development of new vaccines, diagnostics and antimicrobial agents, as well as measures to make these accessible and affordable
- Proposed actions include comprehensive measures to promote increased R&D targeted to the greatest public health needs and introduction of regional and global mechanisms to overcome pipeline, production, distribution, and access bottlenecks

UNITED NATIONS

79th United Nations General Assembly (UNGA) High-Level Meeting on Antimicrobial Resistance (September 26, 2024; New York), where global leaders adopted a political declaration that:[7, 8, 9]

- Recognizes that AMR is one of the most urgent global health threats and development challenges, demanding immediate action
- Notes with concern that the R&D pipeline for vaccines, diagnostics, and antimicrobials (especially antibiotics) and alternatives is insufficient
- Made commitments including: exploring, encouraging and promoting innovative incentives and financing mechanisms; recognizing the role played by the private sector in R&D; and continuing to support initiatives and mechanisms to separate the cost of development from the price and volume of sales to support conservative, appropriate use of new therapies.

"Understanding these dynamics and by creating detailed patient persona and empathy maps"

Challenges in the clinical development of new antibiotics

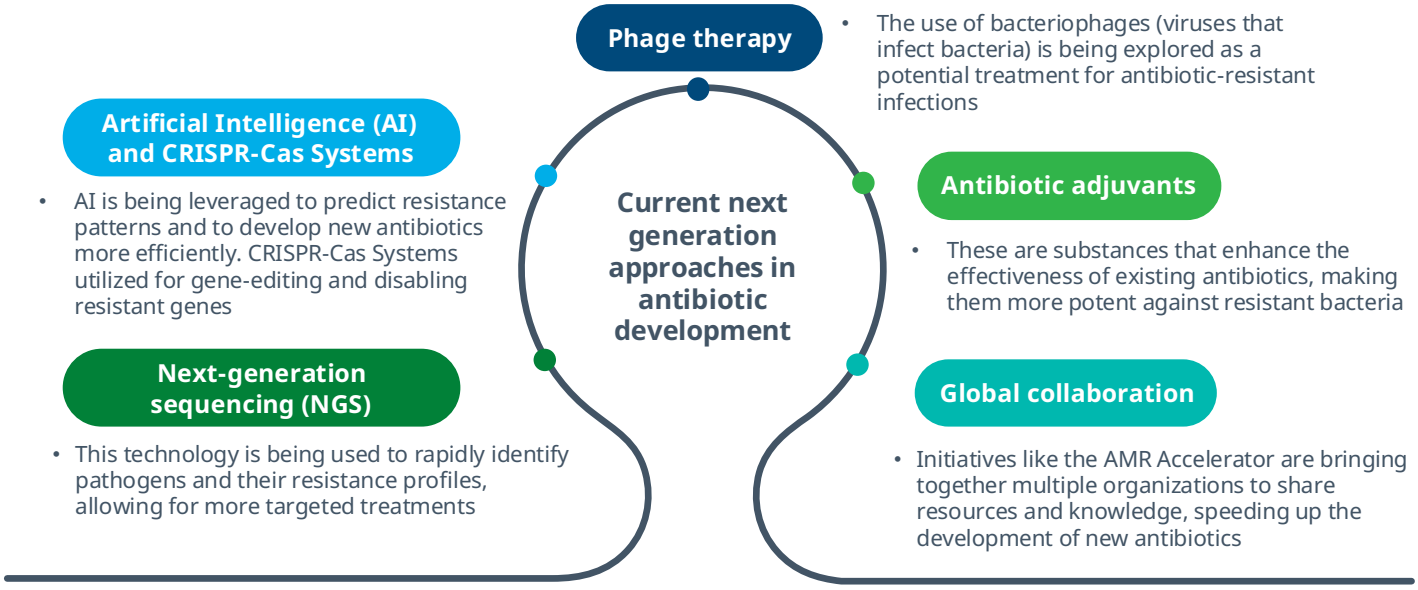
Challenges in antibiotic R&D include:

- **Long development time:** Development of antibiotics can take upwards of 12-15 years.[10] Since 2021, 10 out of 12 antibiotics approved were in existing classes of antibiotics with established patterns of resistance.
- **High development costs:** Antibiotic studies can be lengthy as a result of low recruitment rates due to requirements to recruit patients with infections caused by multi-drug resistant pathogens and challenging entry criteria. In the United States, antibacterial Phase I trial initiations fell by 46% in 2016-2020 compared with 2011-2015, according to a 2022 report;[11] Phase II and III trial initiations fell by 33% in the same period. Secondly, trials may not be conducted in areas of truly high prevalence and unmet need to due to the challenges of providing consistent surveillance/ availability of antibiogram data, and access to rapid diagnostics.
- **Challenging study designs and regulatory approval:** Many antibiotic studies have a non-inferiority design. For instance, the use of a placebo control group poses ethical challenges, with comparison to existing treatments required to avoid denying access to existing treatments. Non-inferiority designs require a large sample size, which directly coincides with extensive enrollment durations. These designs can be cost-prohibitive. Limited Population Antibiotic Drug (LPAD) regulatory approval has gained traction in recent years allowing a smaller sample size and more sustainable costs. However, potential therapies targeting a single pathogen require equitable access to diagnostics to confirm the presence of the pathogen, which may be challenging in low- and middle-income countries (LMICs) and offer narrow indication approvals.[12]
- **Clinical trial success rates:** These have historically been low for antibiotics, due to the many challenges involved in this field. For example, the statistical data requirements, as well as the need for microbiological evidence, in antibiotic trial designs adds to the complexity and overall lower approval success rate. However, the success rate for new antibiotics moving from Phase I through to U.S. Food and Drug Administration approval in 2011 to 2020 totaled 16.3%, compared with 7.9% for the pharmaceutical industry overall.[12]
- **Post-approval challenges:** Single pathogen assets limit what can be treated, while emergence of resistance can be seen in as little as one-year post-marketing. The ever-changing landscape of antimicrobial resistance results in chasing a moving target globally, with granular and comprehensive data either lacking or unavailable to support monitoring and R&D efforts. Heavy reliance on antimicrobial stewardship programs and guidelines results in a countereffect, forcing the focus on antibiotic development of assets with a narrow spectrum of activity, where in the absence of systematic and equitable access to diagnostics in routine practice provides yet another challenge to overcome. This increases the financial strain on companies, while reducing the overall scientific advances within the antibiotic pipeline.

Next-generation approaches to development

As shown in Figure 1, current approaches that may help overcome challenges and address unmet needs in antibiotic development include: next-generation sequencing (NGS), which is being used to rapidly identify pathogens and their resistance profiles, allowing for more targeted treatments; artificial intelligence (AI) and CRISPR-Cas Systems, with AI being leveraged to predict resistance patterns and develop new antibiotics more efficiently, and CRISPR-Cas Systems being used for gene-editing and disabling resistant genes; [13] phage therapy, which involves the use of bacteriophages (viruses that infect bacteria), is being explored as a potential treatment for antibiotic-resistant infections; and antibiotic adjuvants, which enhance the effectiveness of existing antibiotics, making them more potent against resistant bacteria.

Figure 1: next generation approaches to antimicrobial development



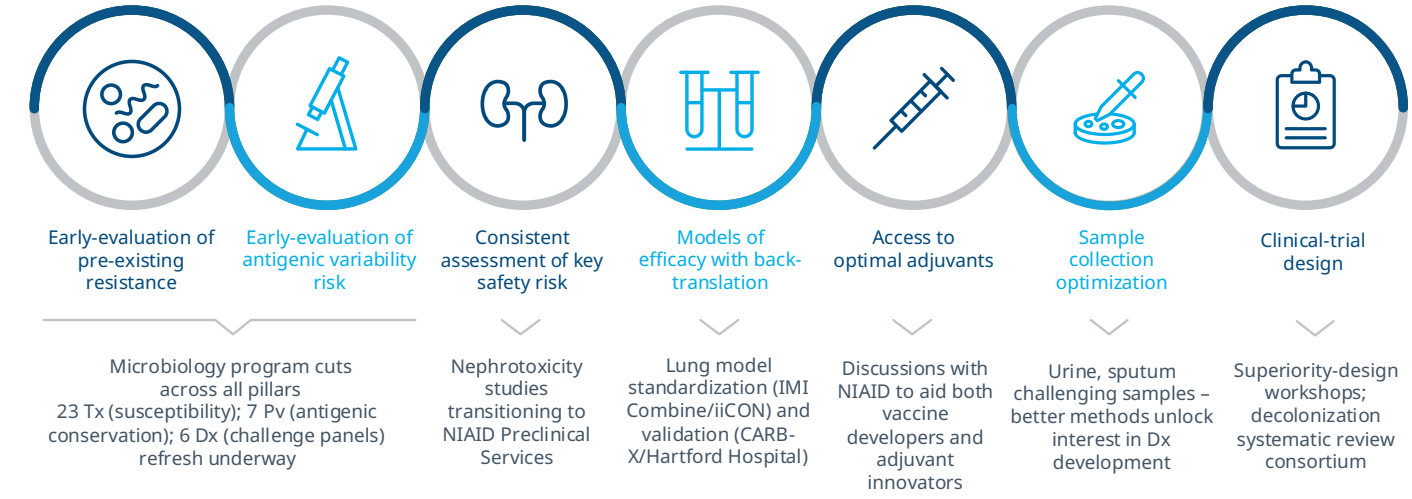
Global collaboration drives advances

Global collaboration will be key to future advances. One successful example of global collaboration is the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), a non-profit partnership with over $900 million in funding from a consortium of governments and foundations.[14] Headquartered at Boston University, CARB-X is a multilateral initiative supported by governments and private foundations, including: the US Biomedical Advanced Research and Development Authority (BARDA); Wellcome Trust; Germany's Federal Ministry of Education and Research (BMBF); the UK Department of Health and Social Care (DHSC); the Bill & Melinda Gates Foundation; the Public Health Agency of Canada (PHAC); the Novo Nordisk Foundation; and the US National Institute of Allergy and Infectious Diseases (NIAID).[15]

Founded in 2016, CARB-X aims to address the National Action Plan for Combating Antibiotic-Resistant Bacteria's goal 4 ("to accelerate basic and applied R&D for new antibiotics, other therapeutics and vaccines").[16] The organization funds early discovery, preclinical and Phase I studies for therapies and vaccines. For diagnostics, CARB-X funds evaluations of feasibility through completion of alpha-development.

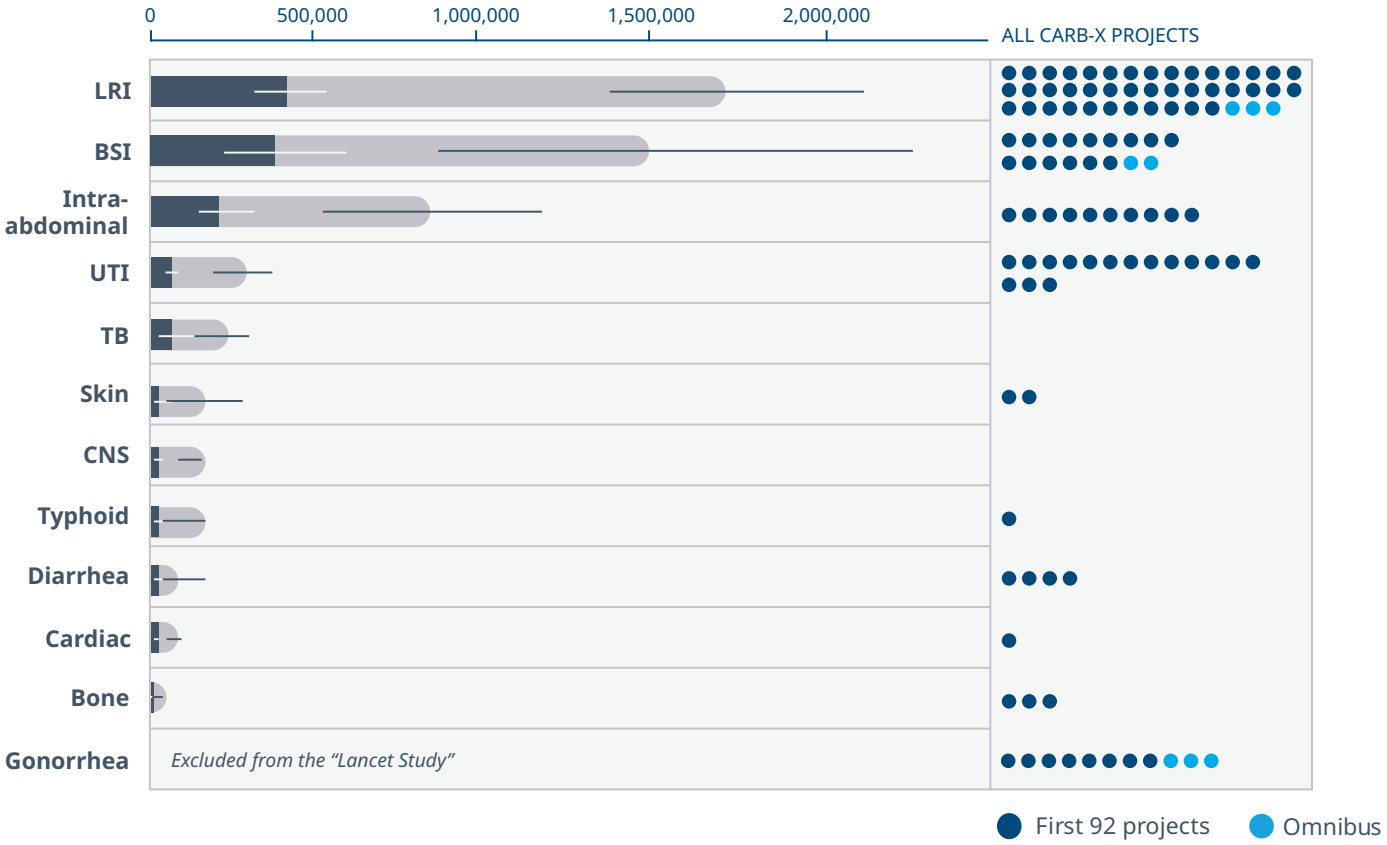
CARB-X issues open calls with specific themes for proposals from product developers. Suitable proposals are recommended by external advisors and approved by the CARB-X investment committee. Projects are funded in stages, with external advisors evaluating milestone achievement and the CARB-X investment committee checking on ongoing portfolio fit. CARB-X also provides non-financial support to accelerate projects. Programs focus on bringing data and tools to the portfolio, including a range of topics as shown in Figure 2.

Figure 2: CARB-X programs aim to overcome program hurdles



The CARB-X portfolio focuses on areas of high global burden and unmet needs (Figure 3).[17] CARB-X has supported 104 R&D projects in 13 countries.[18] Of these, 18 projects are undergoing or have completed clinical trials; 12 are active in clinical development, including late-stage clinical trials; and two diagnostics have reached the market.

Figure 3: CARB-X portfolio



Innovative funding mechanisms: overview of UK Antimicrobial Products Subscription Model

Looking ahead, innovative funding mechanism approaches are needed to ensure sustainable investment in AMR solutions, including the development of novel antibiotics and other anti-bacterial therapies. One initiative that aims to incentivize development of new antimicrobials by providing pharmaceutical companies with a guaranteed income stream regardless of quantities sold is the UK Antimicrobial Products Subscription Model.[19] This model is known as form of "pull" incentive, designed to account for the fact that antimicrobial research can otherwise be unattractive for companies due to high R&D costs and low returns due to the need to restrict antibiotic use.[20] The Subscription Model is designed to prevent the overuse of new therapies by paying companies a fixed annual fee for antimicrobials based on their value to the National Health Service (NHS) rather than by volumes used.

Conclusion

An impactful response to AMR relies on investment in innovative medicines, access to effective therapies in an equitable manner, and availability of comprehensive data to guide interventions. Incentives to stimulate and maintain antibacterial R&D requires novel approaches to ensure sustainable investment.

Availability of data is critical to every point of the response to AMR, with a pressing need to invest in the infrastructure needed to generate essential data and fill knowledge gaps.[21] Additionally, health economic modelling can help quantify the impact of AMR to demonstrate the need for investment and action now.

Promising steps forward, such as the UK Antimicrobial Products Subscription Model and the projects supported by CARB-X, could be adopted more broadly. These can help incentivize antimicrobial development while preserving the utility of new and existing products to the maximum extent possible – providing real hope in addressing of AMR effectively.

Looking ahead, there is an opportunity to associate clinical trials with public health need by conducting studies in regions where the AMR burden is greatest, while ensuring that these trials meet appropriate evidentiary standards. This approach offers a real opportunity to innovate to overcome challenges and bring new therapeutic options to all.

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Sharon Hughes has over 29 years of industry experience spanning both clinical research and R&D formulations. She has a deep focus on respiratory infectious diseases, specifically on community-acquired and ventilator-acquired pneumonias, as well as studies involving antimicrobial resistance and invasive fungal infections in vulnerable HSCT and immunocompromised populations. Sharon has over a decade of experience managing clinical trials and developing therapeutic strategies around VABP/HABP/CABP and VRE/CRE-related infection protocols.

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Rachel Freeman is an infectious disease epidemiologist by training with over 15 years of experience working in the field of antimicrobial resistance (AMR). She has held positions across several sectors including healthcare, academia, public health, and industry. Rachel is passionate about incorporating data into solutions designed to tackle AMR and has spent the majority of her career implementing surveillance systems and optimizing data collection. Rachel is leading IQVIA's AMR Strategy, including the development of innovative solutions and offerings that integrate real-world data into decision making. She is an advocate for the need for cross-sectoral and transdisciplinary working in addressing the threat posed by AMR and is leading engagements with national bodies and the life sciences industry in support of generating valuable data assets that may be used to provide powerful insights.

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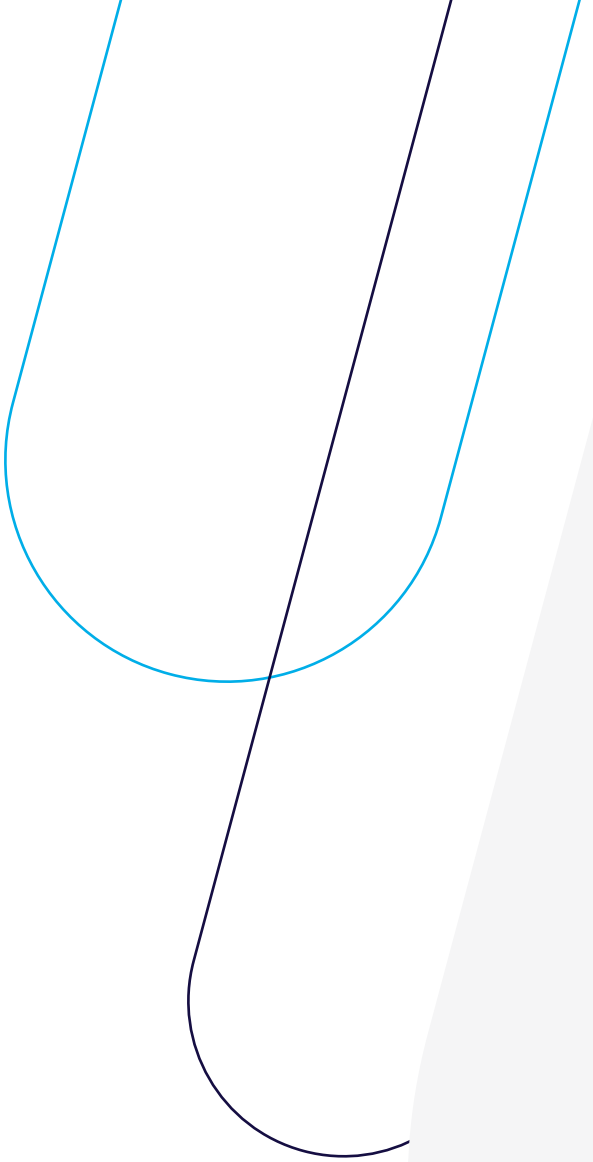
Erin Duffy, PhD, is the Chief of Research & Development at CARB-X, a global biopharmaceutical accelerator for the discovery and early development of products to prevent, diagnose and treat bacterial infections. Erin is an expert in drug discovery and problem solving in the antibiotic arena. Most of her professional growth was with Melinta Therapeutics (founded as Rib-X Pharmaceuticals), where over 17 years she became Executive Vice President, Chief Scientific Officer and R&D site head. Her entry into the pharmaceutical sector began with Pfizer Central Research. Erin's formal training was at Yale University, where she completed a PhD in physical-organic chemistry and an HHMI postdoctoral fellowship in computational structural biology.



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