

The Role of the Innovation Ecosystem in Overcoming the Misaligned Incentives that Plague the Development of Medicines to Combat Antimicrobial Resistance



The world urgently needs new antimicrobials to help fight the rise of drug-resistant bacterial and fungal infections. Antimicrobial Resistance (AMR) is an ongoing public health crisis that affects at least 3 million Americans and results in 48,000 deaths annually.¹ The World Bank Group's 2017 report on drug-resistant infections estimates that unless action is taken, AMR could take 10 million lives annually by 2050, a higher death toll than from cancer.² If we fail to address the crisis, many modern medical advancements that depend on antibiotics—such as routine surgery, cancer therapy and treatment of chronic disease, may be jeopardized.



Unfortunately, current treatments were not developed to treat resistant strains and the pipeline of new antimicrobials needed to stem the tide of AMR has been on the decline. Nearly every antibiotic in use today is based on discoveries made more than 33 years ago.³ Meanwhile, drug-resistant bacteria and fungi continue to evolve faster than new antimicrobial medicines can reach the market. Similarly, recent assessments of the pipeline of antibiotics targeting high-risk pathogens also report that though progress has been made, there are still too few potential medicines to meet current and anticipated needs.



Developing medicines is a long, complex and risky process that can take 10–15 years and on average \$2.6 billion just to develop one new medicine. Among all medicines, just 12% entering clinical trials are ultimately successful in obtaining U.S. Food and Drug Administration (FDA) approval. Yet among antibiotics, this process is fraught by even more risk. Developing a single antimicrobial medicine can take anywhere from 10–20.5 years and \$568-\$700 million. And even among antibiotics in existing classes of antibiotics in preclinical development, just 1 in 15 will ultimately be approved and reach patients. And among new classes of antibiotics, just 1 in 30 are ultimately successful.⁴



The fundamental problem with developing new medicines to target antimicrobial resistance is, unlike most other medicines, the market is inherently limited by design. In order to slow and control continued antimicrobial resistance, newer medicines are frequently used only in a limited set of circumstances and in only the most necessary cases. This makes it challenging for biopharmaceutical research companies to recoup research and development costs in subsequent sales. Antibiotic stewardship programs are designed to limit the use of new antibiotics specifically for this reason and thus limit the commercial viability of new antimicrobials.



Unfortunately, our current reimbursement system also reinforces misguided incentives which discourage the appropriate use of new antimicrobials and favor older medicines that have been around for decades but may be less effective in meeting current AMR threats. That is because newer antimicrobial medicines are often more expensive than older medicines, and our bundled payment system creates financial disincentives for hospitals to prescribe these newer medicines, even when they may be more appropriate to treat drug-resistant infections. Ineffective or incomplete use of antimicrobials can also exacerbate AMR.



As a result of these challenges, in recent years several biotechnology companies have declared bankruptcy or exited this space, including those who had successfully developed new antimicrobials.⁵ In fact, while 15 new antimicrobials were approved over the past decade, a third of the companies behind those medicines subsequently filed for bankruptcy or exited the field.⁶

Antibiotic Company Bankruptcies Underscore the Challenging Environment for Developing Medicines to Combat AMR

Recent reports of several high-profile bankruptcies highlight the funding challenges associated with developing these medicines and the lack of commercial sustainability in the market for novel antimicrobial medicines despite the tremendous public health need.

- One of the country's biggest antibiotic specialist companies, Melinta Therapeutics, filed for bankruptcy in 2019. The company cited slow sales growth and high costs. The bankruptcy occurred three weeks after failing to turn a profit on the four antibiotics that were available to treat patients. The filing sparked many companies to reconsider research in this space and prompted investors, executives and doctors to call for an overhaul in how these medicines are paid for.⁷
- Another manufacturer, Aradigm, had acquired and conducted research on a potential antibiotic that ultimately was not approved by the FDA. Aradigm subsequently filed for bankruptcy in 2018. The FDA asked the company to run an additional 2-year Phase 3 clinical trial before resubmitting for approval, a setback the company could not ultimately overcome given the lengthy time and resource requirements. The failure of the antibiotic candidate and resulting bankruptcy led to the sale of Aradigm's overall assets for \$3.2 million to a former investor that had previously paid \$26 million to the company just to acquire a stake in its inhaled antibiotics.⁸
- Achaogen, another antibiotic manufacturer, also declared bankruptcy just one year after it launched a new antibiotic for increasingly difficult-to-treat urinary-tract infections. The product was sold for about \$16 million, a fraction of the hundreds of millions of dollars the company spent bringing the medicine to market over 15 years. Research and development for the antibiotic was also supported through a collaboration with the Biomedical Advanced Research and Development Authority (BARDA), aimed toward improving the government's preparedness for and ability to counter various threats to U.S. public health. The company was awarded \$124.4 million in funding over the lifetime of the research and development program. The medicine became the first antibiotic designated as a breakthrough therapy and later it was added to the World Health Organization's (WHO) list of essential new medicines. According to one of the company's founders, microbiologist Ryan Cirz: "we got everything right, and it still didn't work."^{9, 10}

A Unique Innovation Ecosystem has Evolved to Address the Challenges of AMR

In the 1980s, 18 major biopharmaceutical companies were researching and developing new antibiotics. Today, there is only a handful. About 90% of the companies currently developing antibiotics are small start-up biotechnology companies.¹¹ However, without a viable antibiotic market, these companies are often unable to find financing for early development phases. This means important antibiotics may never overcome the pre-clinical stages of development known as the “valley of death,” where many projects are abandoned due to lack of funding and support. Even those who surpass this hurdle may struggle to find financing or broker acquisition by a larger pharmaceutical company offering the infrastructure necessary to complete costly late-stage clinical trials and the expertise needed to ultimately bring the drug to market.

To address the challenges of early- and late-stage clinical development and to overcome the market’s failure to drive innovation for antimicrobials, innovative partnerships and initiatives within and between the public and private sectors have evolved.



Citation: Adapted from CARB-X and Payne DJ et al., *Drugs for bad bugs: confronting the challenges of antibacterial discovery*. *Nat Rev Drug Discov*. 2007;6(1):29-40; Czaplewski L et al. *Alternatives to antibiotics-a pipeline review*. *Lancet Infectious Dis*. 2016(2): 239-51.

Glossary:

IND: Investigational New Drug Application

NDA: New Drug Application

BLA: Biologic Drug Application

Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X): CARB-X is a global non-profit partnership dedicated to advancing antimicrobial research to tackle the global rising threat of AMR by **accelerating preclinical candidates toward clinical development for dangerous bacteria identified by the WHO and CDC priority pathogen lists**. The ultimate goal of CARB-X is to support the early development of new antibiotics, vaccines, rapid diagnostics and other products so they can attract additional private and public investment. Between 2016 and 2022, the accelerator will fund up to \$480 million to achieve this goal. CARB-X is led by Boston University, funded by U.S. BARDA, the Wellcome Trust, a global charity based in the U.K. working to improve health globally, Germany’s Federal Ministry of Education and Research, the U.K. Government’s Global Antimicrobial Resistance Innovation Fund, the Bill & Melinda Gates Foundation, the world’s largest foundation dedicated to improving the quality of life for individuals around the world, and receives in-kind support from National Institute of Allergy and Infectious Diseases, part of the U.S. National Institutes of Health.

AMR Action Fund:¹² AMR Action Fund is a groundbreaking partnership that seeks to strengthen and accelerate the research and development of antibiotics through investment and provision of industry resources and expertise to biotechnology companies. With funding from over 20 leading biopharmaceutical companies, global foundations and development banks, the AMR Action Fund is the largest public-private partnership supporting the development of new antibiotics.

The AMR Action fund aims to bring 2-4 new antibiotics to patients by 2030 by investing more than \$1 billion in smaller biotech companies and providing industry expertise to support the clinical development of novel antibiotics. The Fund provides a bridging solution to **help biotech companies take their discoveries over the finish line**. Without this type of support and investment in the more complex, expensive later stages of development, these compounds will wither on the vine. The broad alliance of industry and non-industry stakeholders also encourages governments to advance policies that will create market conditions that will encourage a sustainable pipeline of new antibiotics to fight the highest priority bacterial threats over the long term.

Antimicrobials Working Group (AWG): AWG is a coalition of emerging antimicrobials and diagnostics companies. AWG is committed to improving the regulatory, investment and commercial environment for antimicrobial drug and diagnostic device development.¹³

The Partnership to Fight Infectious Disease (PFID): PFID is a group of patients, providers, community organizations, academic researchers, business and labor groups and infectious disease experts working to raise awareness of threats posed by infectious disease. PFID will explore and advance solutions to address the need to enhance pandemic preparedness, address the growing threat of AMR and the need for new antimicrobial treatments and empower informed choice and confidence in COVID-19 vaccines.¹⁴

The Innovation Ecosystem Cannot Solve These Problems in Isolation, Comprehensive Policy Reforms are also Needed

While recent policy changes have enhanced the research ecosystem and provided support and incentives for researchers to develop new antimicrobials, additional policy reforms are needed to create a more sustainable environment for antimicrobial R&D and commercialization to ensure a robust pipeline for future treatments.

To safeguard our future from the global threat of AMR, congress and relevant government agencies should act by:

- Addressing the reimbursement barriers in the inpatient bundled payment system in Medicare by creating a separate payment mechanism;
- Advancing legislative and administrative policies that create a competitive return on investment after marketing approval to encourage a diverse pipeline of new medicines;
- Supporting policies that reduce barriers and speed the process of developing promising new ideas and investigational drugs into products that benefit patients;
- Advancing innovative payment mechanisms to maintain access while not driving overuse; and,
- Ensuring comprehensive stewardship programs and surveillance mechanisms to support appropriate use and public health management of medicines to address AMR.

Endnotes

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