

Targeting antimicrobial resistance

Funding for early-stage projects and global collaborations are aiming to breathe life into the fragile ecosystem for novel antibiotics.

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For many years, antimicrobial resistance (AMR) has been recognized as a serious threat to public health, and the problem is getting worse. Bacteria have developed resistance to once-innovative antibiotics—and now, owing partly to their overuse—there are increasingly limited options for combating a growing number of bacterial pathogens that cause serious infections.

Despite this impending crisis, the development of new antibiotics has long been stuck in a rut, largely owing to the lack of a sufficient market for new antibiotics. Consequently, larger pharma companies have exited the field or downsized their involvement in it to focus on other therapeutic areas, and smaller companies working in the field have struggled to make a return on their investments, even when they have managed to overcome the substantial challenges to bring a novel antibiotic

to market. The fragile antibiotic innovation ecosystem and the failed market for new drugs have created the perfect storm, and an urgent need for action. Here, we highlight the role of dealmaking (Table 1), partnerships and global initiatives (Fig. 1) in tackling the AMR crisis.

Sparse development pipeline

AMR remains a looming threat because the continual emergence of antibiotic resistance is outpacing the emergence of new antibiotics from the weak development pipeline. The problem is particularly acute for Gram-negative pathogens, such as *Acinetobacter baumannii*, for which it is inherently harder to develop new antibiotics because of the structure of their cell wall. Agents with new mechanisms of action could be especially useful

Table 1 | Selected recent deals related to the development of antibacterial therapies

Date	Companies	Deal summary	Deal value (\$ million)
August 2021	Eagle Therapeutics, Combioxin	Eagle Pharmaceuticals licenses commercial rights to Combioxin's novel liposome-based antitoxin agent, CAL02, intended to treat severe pneumonia in combination with traditional antibacterial drugs. The therapy is ready for phase 2b/3 development. The deal includes an upfront payment of \$10 million to Combioxin and up to \$105 million in milestone payments.	115
July 2021	Pfizer, Spero Therapeutics	Spero Therapeutics signs agreement with Pfizer for SPR206 to treat multi-drug resistant Gram-negative infections. The deal includes a \$40 million equity investment by Pfizer, and Spero is eligible to receive up to \$80 million in milestones for rights to SPR206, a next-generation polymyxin candidate that has entered phase 1 development.	120
July 2021	Aridis Pharmaceuticals, AstraZeneca	Aridis licenses AstraZeneca's phase 2 candidate suvratumab, a monoclonal antibody targeting the <i>Staphylococcus aureus</i> alpha toxin, for the treatment of pneumonia. The deal includes an upfront payment of \$11 million to AstraZeneca and up to \$115 million in potential milestones.	126
November 2020	Felix Biotechnology, TFF Pharmaceuticals	Felix signs a letter of intent to collaborate with TFF to use its thin film freezing technology to develop an inhaled bacteriophage-based therapeutic for bacterial lung infections. The agreement includes upfront and milestone payments to TFF Pharmaceuticals of up to \$281 million.	281
January 2019	Janssen Pharmaceuticals, Locus Biosciences	Locus signs collaboration and licensing deal with Janssen for the development of targeted antibacterial therapies based on CRISPR-Cas3-enhanced bacteriophage. The deal includes an upfront payment of \$20 million to Locus, and up to \$798 million in milestone payments.	818
October 2018	Menarini Group, Melinta Therapeutics	Menarini acquires exclusive rights from Melinta to co-develop and commercialize Vabomere (meropenem and vaborbactam), Orbactiv (oritavancin), and Minocin (minocycline) for injection in 68 countries outside of the US. Melinta will receive an upfront payment and milestone payments potentially totalling up to \$265 million.	265
April 2018	Zai Lab, Entasis Therapeutics	Zai Lab signs licensing deal with Entasis to develop and commercialize ETX2514, a novel broad-spectrum inhibitor of β -lactamases in phase 2 development in combination with sulbactam to treat carbapenem-resistant infections, in the Asia-Pacific region. The deal includes an upfront payment of \$5 million to Entasis, and up to \$98.6 million in milestone payments.	104

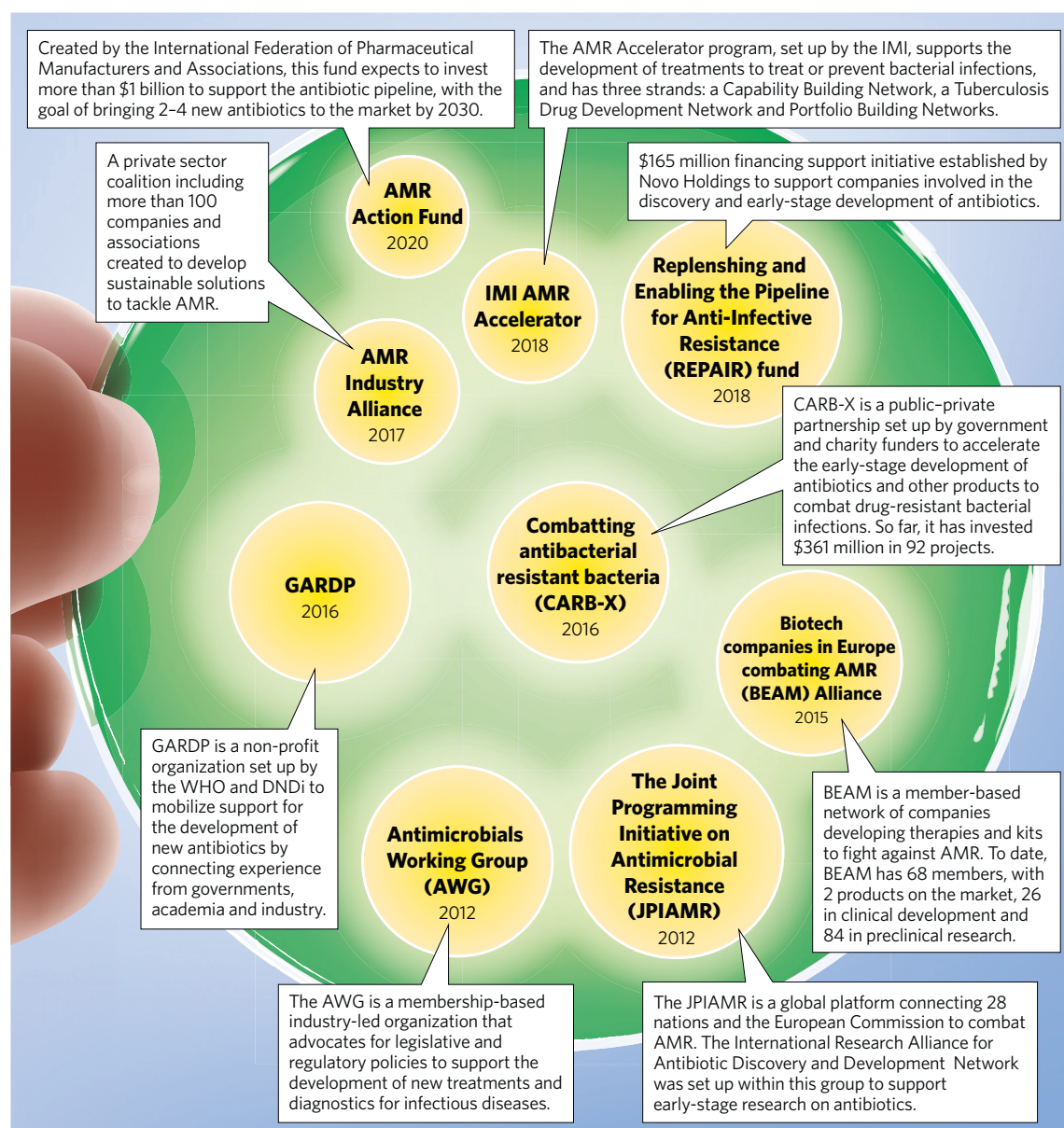


Fig. 1 | Selected initiatives set up to support the fight against AMR. AMR, antimicrobial resistance; DNDi, Drugs for Neglected Diseases initiative; GARDP, The Global Antibiotic Research and Development Partnership; IMI, Innovative Medicines Initiative.

in combating AMR, but the last entirely new class of antibiotics was discovered in the 1980s (*Nature* **586**, S50–S52; 2020).

Indeed, many of the new therapies in development lack novel mechanisms of action. According to the Pew Charitable Trust, 43 antibiotics were in clinical development in March 2021, with around half having the potential to treat infections caused by high-priority Gram-negative bacteria. However, only ~25% of the 43 agents represent a novel drug class or mechanism of action, and none of this subset targeted the high-priority Gram-negative pathogens.

Pipeline partnerships to the fore

With the aim of helping to address the withdrawal of large pharma companies in the field, several initiatives have been established in the past decade to catalyze early-stage research and development (R&D) for novel antibacterial agents (Fig. 1). For example, CARB-X—a global public–private partnership with funders including the US government, the Wellcome Trust and the AMR Centre in the UK—launched in 2016 to support the progression of innovative antibacterial agents into clinical trials. So far, it has invested

US\$361 million in 92 projects, including conventional antibiotics as well as other antibacterial approaches such as phage-based therapies.

However, even with such support for early-stage pipelines, it has become apparent that unless the factors underlying the market failure for antibiotics are addressed, there will be a continued lack of companies prepared to make the substantial and high-risk investments in later-stage clinical trials to bring products to market. Recognizing this problem, 24 pharmaceutical companies came together in 2020 to launch the AMR Action Fund, with the aim of investing \$1 billion in small biotech companies over the next 8–12 years to support 15–20 phase 2 and 3 trials of novel antibiotic candidates (*Nat. Rev. Drug Disc.* **19**, 575–576; 2021).

Encouragingly, there are early hints in dealmaking activity that efforts to support antibiotic R&D could be having an impact. For example, in July this year, Pfizer made a \$40 million equity investment in Spero Therapeutics—a company that has received support from CARB-X—and entered into a licensing agreement for SPR206, a next-generation polymyxin candidate in development to treat serious multi-drug-resistant Gram-negative infections.