nature medicine

Review article

https://doi.org/10.1038/s41591-024-03218-w

Advancing global antibiotic research, development and access

Received: 27 March 2024

Accepted: 30 July 2024

Published online: 3 September 2024

Check for updates

Laura J. V. Piddock[1] ✉, Yewande Alimi[2], James Anderson[3], Damiano de Felice[4], Catrin E. Moore[5], John-Arne Røttingen[6], Henry Skinner[7] & Peter Beyer[1]

The pipeline of new antibiotics is insufficient to keep pace with the growing global burden of drug-resistant infections. Substantial economic challenges discourage private investment in antibiotic research and development (R&D), with a decline in the number of companies and researchers working in the field. Compounding these issues, many countries (from low income to high income) face a growing crisis of antibiotic shortages and inequitable access to existing and emerging treatments. This has led to an increasing role for public and philanthropic funding in supporting antibiotic R&D via the creation of nonprofit public–private partnerships, including Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global Antibiotic Research and Development Partnership (GARDP), industry support for the AMR Action Fund, and pilot schemes to evaluate and reimburse antibiotics in innovative ways. Now is the time to raise the urgency, ambition and commitments of the world's leaders to fully support the antibiotic R&D ecosystem, incentivizing all sectors to conduct public health-driven antibiotic R&D and make effective antibiotics accessible to all who need them.

In 2019, there were 4.95 million deaths associated with drug-resistant infections, including 1.27 million directly attributable deaths[1]. Data from a study by the Global Leaders Group on Antimicrobial Resistance indicate that life expectancy globally will be reduced by 1.8 years over the next decade without specific action to address antimicrobial resistance (AMR)[2]. In 2017, the World Health Organization (WHO) identified a list of 12 antibiotic-resistant bacterial species to be urgently prioritized for drug development[3] and recently updated this list on the basis of shifting patterns of resistance and unmet clinical needs[4]. Nine Gram-negative bacterial species pose the greatest threats to human health, but there are substantial scientific challenges to discovering new drugs with good activity for such bacteria[5]. Unfortunately, resistance is not always reversible, and withdrawal of the antibiotic driving the selection of resistant clones does not always lead to a reduction in the rates of resistance[6]. Even when there is an appropriate and effective antibiotic for a given infection, it may be difficult to use, in short supply or completely unavailable outside a few high-income countries (HICs).

The antibiotic pipeline remains insufficient for current and anticipated future needs; so there continues to be an urgent need to develop innovative antimicrobials[7]. In the past decade, all major policy reports recommending priority actions to address AMR have recognized the pressing need to close the funding gap for antibiotic research and development (R&D). This has led to public and philanthropic funding playing an increasing role in supporting antibiotic R&D, including via 'push' mechanisms (financial support for innovation, including via nonprofit public–private partnerships) and 'pull' mechanisms (financial reward for new, needed antibiotics that enter the market) that complement each other and aim to attract sufficient private R&D investment[8–11].

[1]Global Antibiotic Research and Development Partnership (GARDP), Geneva, Switzerland. [2]Africa Centres for Disease Control and Prevention (Africa CDC), Addis Ababa, Ethiopia. [3]International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Geneva, Switzerland. [4]CARB-X, Boston University School of Law, Boston, MA, USA. [5]Centre for Neonatal and Paediatric Infection, St George's, University of London, London, UK. [6]The Wellcome Trust, London, UK. [7]AMR Action Fund, Boston, MA, USA. ✉e-mail: lpiddock@gardp.org

In this Review, we discuss how antibiotic use is linked to the escalating global problem of AMR and how strategies to tackle this create a unique and unfavorable R&D landscape. We discuss potential solutions, including the growing importance of not-for-profit partnerships across the product development lifecycle and the merits of both push funding and pull incentives in supporting a healthy ecosystem of antibiotic innovation. We highlight the importance of complementary efforts to enhance global access to new and existing antibiotics and the role of policymakers and politicians in ensuring that the needs of all populations can be addressed sustainably over the long term.

Antibiotic use and AMR

The use of antibiotics in people and animals is an important driver of individual and global levels of AMR affecting human health. However, the link between antibiotic use and drug resistance is complicated, and there are many confounding factors, including the site of infection, differences between bacterial species and how they respond to different drugs and dosing strategies[12], that make generalizing and predicting any future resistance to individual drugs difficult.

Reducing the incidence of AMR relies on addressing the drivers that promote resistance and developing new treatments. As any use, but especially overuse and inappropriate use of antibiotics, facilitates resistance, strategies for appropriate stewardship and equitable access should be assessed and used to support R&D. These strategies rely on up-to-date information on the types, rates and spread of resistance, which are not always consistent.

Antibiotic stewardship

The WHO AWaRe classification of antibiotics[13] is a tool to support antibiotic stewardship efforts at local, national and global levels, with antibiotics classified as 'Access', 'Watch' or 'Reserve' on the basis of their impact on AMR. This can be a useful tool for monitoring antibiotic use and consumption, defining targets and monitoring the effects of stewardship policies that aim to optimize antibiotic use and curb AMR. The WHO 13th General Programme of Work 2019–2023 included a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics; this was increased in the European Union (EU) to 65% in 2023 (ref. 14). According to the WHO, the first indication of clinical resistance is typically reported within 2–3 years following market entry of a new antibiotic[15], hence their recommendation to use Access antibiotics when possible as an empiric therapy (thereby delaying the use of new drugs and the emergence of resistance to them). In line with antibiotic stewardship and to protect against overuse of new antibiotics when they first come to market, policymakers have recognized that the development of new treatments relies on funding instruments and incentives that delink the return on investment in R&D from the volume of antibiotics sold.

The burden of AMR

Measuring the susceptibility of bacteria to antibiotics is essential to inform appropriate clinical use of antibiotics (including stewardship programs and treatment decisions at the individual level) and to enable surveillance and quantification of AMR in a standardized way. In most clinical microbiology laboratories, the testing methodology has not substantially changed for decades and relies on detecting phenotypic resistance in vitro following international guidelines, such as those of the European Committee on Antimicrobial Susceptibility Testing (https://www.eucast.org) and the Clinical and Laboratory Standards Institute (https://www.clsi.org). For public health purposes, there have been challenges in extrapolating antibiotic susceptibility data across local, national and international geographies because of inconsistencies in the methods and antibiotics tested and because results may reflect local resistance to a few drugs only. The WHO Global Antimicrobial Resistance and Use Surveillance System (https://www.who.int/initiatives/glass) collates antibiotic surveillance results from countries that share them (an increasing number each year), supporting the utility of sharing these data. The Global Antimicrobial Resistance and Use Surveillance System also collects data on antimicrobial use and clinical data to inform on the burden of AMR globally.

Data that inform estimates of the current burden of AMR are limited by many factors, including sparse coverage across some regions (such as the WHO African Region), inconsistent interpretation of MDR, XDR and PDR (described in Box 1) and data deriving from tertiary hospitals with microbiology laboratories versus community settings. Despite these limitations, the Global Research on Antimicrobial Resistance Project has provided the most accurate data so far, with an analysis of 23 bacterial pathogens and 88 pathogen–drug combinations[1]. According to this analysis, drug-resistant lower respiratory infections accounted for more than 1.5 million deaths, with six bacterial species responsible for 73.4% of the deaths. The burden was not spread equally among demographic groups or geographies; those most impacted were babies and children, irrespective of country. Death rates were highest in western sub-Saharan Africa (at 27.3 deaths per 100,000) and lowest in Australasia (6.5 deaths per 100,000 persons).

The incidence of drug-resistant bacterial infections is higher in areas of high antibiotic use and low vaccination coverage (whether from low uptake or poor access) and in areas with lack of access to clean water, poor sanitation, high population densities, poverty, conflict and population migration[16]. Rates are lower in areas with high-quality public health and infection-control systems[17]. However, not all vaccines are universally available[18] and only exist for some bacterial pathogens prone to drug resistance. Also, good infection and prevention control (IPC) is not always possible in all settings[19], and good antimicrobial stewardship is challenging to implement globally due to differences in healthcare[20]. Resistance is an inevitable consequence of use; so there will be a continual need to develop the next generation of treatments and make them accessible and affordable to all who need them as part of universal health coverage.

Why is the antibiotic pipeline so poor?

The period between the 1950s and the 1980s is often referred to as the 'golden era' of antibiotic drug discovery, with many new classes being developed during this time. This was followed by a period of steep decline, during which there was a greater focus on developing new agents within existing classes (rather than new classes of drugs) to counter the growing problem of resistance[21]. Gradually, the pharmaceutical industry disinvested, and, by the early 2000s, when methicillin-resistant *Staphylococcus aureus* reached epidemic levels

BOX 1

Defining AMR

Magiorakos et al.[86] proposed the following pragmatic definitions to categorize resistance: (1) multidrug resistant (MDR), bacteria resistant to at least one agent in three or more antimicrobial categories; (2) extensively drug resistant (XDR), bacteria resistant to at least one agent in all but two or fewer antimicrobial categories (bacteria are susceptible to only one or two antibiotic categories); and (3) pan-drug resistant (PDR), bacteria resistant to all agents in all antimicrobial categories. The term difficult-to-treat resistance (DTR) has also been used to describe Gram-negative bacteria that are resistant to first-line antibiotics where the only useful treatments are less effective or more toxic 'Reserve' agents; because of the difficulty in treating these patients, their infections may have higher mortality[87].

https://doi.org/10.1038/s41591-024-03218-w

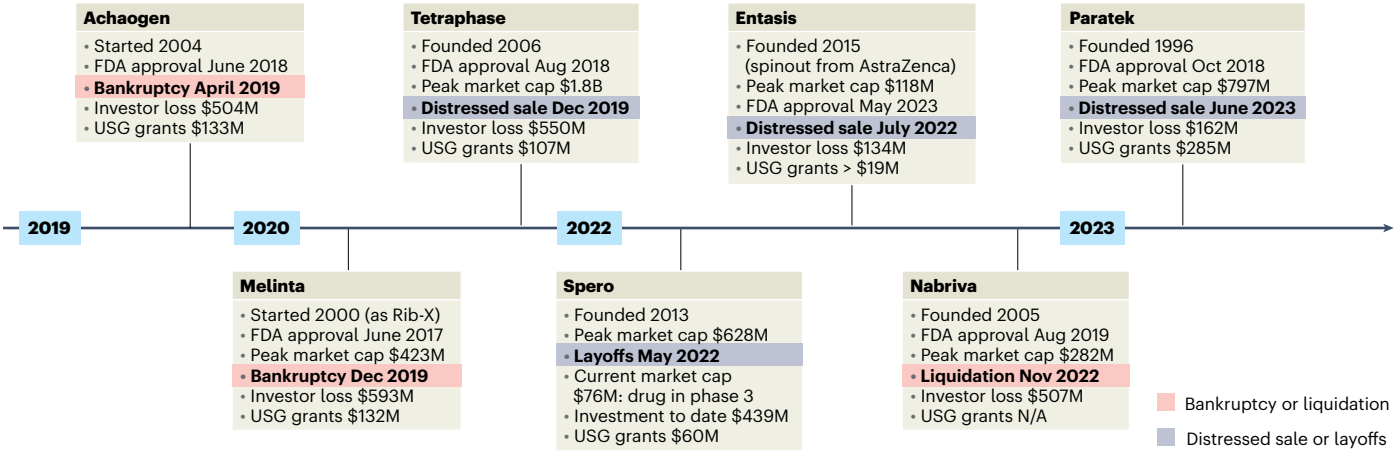

Fig. 1 | Financial problems of antibiotic SME (biotech) companies. Bankruptcy or liquidation (red shading) and distressed sales (blue shading) are common among small-to-medium-sized antibiotic development companies. Data are current as of third quarter 2023 and subject to change as market conditions evolve. Cap, capital; M, million. USG, United States government; N/A, no information available.

in certain regions and hospitals, it became clear that there were not enough new appropriate antibiotics in the pipeline.

Lack of innovation

Between 2010 and 2019, regulatory authorities have approved an increasing number of new antibiotics[22], although a WHO analysis (https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/antimicrobial-resistance/analysis-of-the-antibacterial-pipeline) indicated that there were few real innovations and limited added value over the current standard of care. Furthermore, the clinical pipeline remains inadequate to keep pace with the global burden of drug-resistant infections. As of 2022, the WHO reported 11 small-molecule antibiotics and 13 non-traditional treatments in late-stage clinical trials (phase 2 or 3) and one in pre-registration (clinical trials completed and data submitted for approval to use the drug in patients), all with activity against one or more WHO priority pathogens and which, if adequately funded and successful, could launch in the next 3–5 years. There was only one antibiotic candidate active against all four 'critical' priority pathogens in phase 3, and, for five of the seven high-priority pathogens, there are between 0 and three antibiotics in any stage of development. However, of 12 that fulfill the WHO innovation criteria, only four were active against 'critical priority' pathogens[23]; most are existing drugs combined with a 'resistance breaker', such as a β-lactamase inhibitor, and therefore are not new classes or agents with new modes of action. The preclinical pipeline is more promising, but many products at this stage of development are so innovative that they have no clear financial and clinical development path. Furthermore, innovative approaches often require higher levels of risk and investment.

Lack of investment and poor returns

While developing new antibiotic classes proved to be increasingly challenging from a scientific point of view, the lack of investment into antibiotic R&D, particularly private investment in small–medium-sized companies (SMEs/biotechs), is a direct result of the lack of economic returns to companies and investors that successfully develop new antibiotics. The estimated cost up until first approval for one antibiotic is over US $1 billion, accounting for attrition and cost of capital, whereas the expected return is less than $100 million per year[24].

To our knowledge, there are only six moderate-to-large companies (GSK, MSD, Otsuka, Pfizer, Roche and Shionogi) with active antibiotic programs. Antibiotic R&D, particularly from discovery to preclinical stages, is typically carried out in academia or SMEs, with the latter sometimes doing clinical development as well. There are more than 50 SMEs working on new treatments for drug-resistant infections[24,25] (https://beam-alliance.eu/), but, according to the WHO, nearly half of these companies (often spinouts from universities) have fewer than ten employees and less than 12 months of funding[23].

This contrasts with R&D ecosystems of other therapeutic fields, in which academic and publicly funded research is taken forward by a mix of small and large companies, with substantial capital investment from venture capital firms and institutional investors. Larger companies become involved if the data look promising, bringing the scale of investment and capabilities needed for late-stage development, global regulatory submission and commercialization. This system does not work effectively for antibiotics because, despite promising data, these products remain financially unattractive and struggle to attract sufficient private investment to complete development of their programs and enter the market. This can result in promising new innovations getting stuck in a 'valley of death' and not progressing to regulatory approval.

A high-risk market

Even when SMEs manage to secure investment for phase 2 and 3 studies and successfully gain regulatory approval, economic challenges persist. Of the last ten antibiotics reaching market, seven of the companies that launched them have either gone bankrupt or succumbed to a distressed sale (Fig. 1). Possible reasons for the failure of these new antibiotics to achieve sustainable sales include a lack of real innovation or response to unmet medical needs and insufficient clinical data to convince healthcare professionals to prescribe the new (high-cost) drug over the standard of care[26]. Also, importantly, new antibiotics are typically classified as 'Reserve' and so are used sparingly. Investors in these companies have lost billions of dollars as a result. For SMEs that launch an antibiotic, the low potential for sales can be a death knell.

Biotechnology investors are adept at assessing and managing the risks and hefty expense of product development. It is therefore a rational consequence of the unique economics of the antibiotic market that most investors, including venture capital firms and larger pharmaceutical companies, have scaled back antibiotic R&D investment considerably. Between 2011 and 2020, US biotech companies developing antimicrobials raised $1.6 billion, compared with $26.5 billion raised by oncology companies in venture capital funding during the same period[27]. Most private investment goes to areas such as chronic diseases or cancer, with greater probability to earn a positive investment return.

https://doi.org/10.1038/s41591-024-03218-w

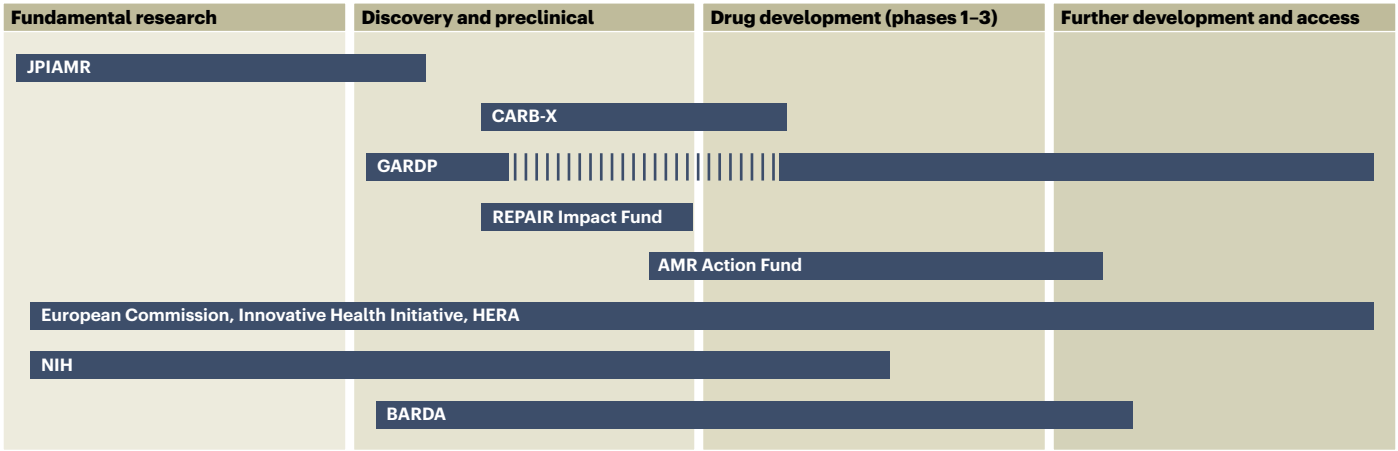

Fig. 2 | International push mechanisms covering all phases of antibiotic R&D. Public actors at the national and regional level include the NIH, the Biomedical Advanced Research and Development Authority (BARDA), the JPIAMR and the European Commission. Global nonprofit organizations include CARB-X and GARDP. For-profit impact investors include the REPAIR Impact Fund and the AMR Action Fund. These are for illustration purposes and are not an exhaustive representation. HERA, Health Emergency Preparedness and Response Authority; NIAID, National Institute of Allergy and Infectious Diseases.

Strategies for a sustainable antibiotic R&D ecosystem

In response to the limited antibiotic pipeline and the many obstacles hindering discovery and R&D, governments, philanthropies and the private sector have proposed and/or implemented push mechanisms and pull incentives. Below, we highlight those funding instruments and incentives already in place.

Push mechanisms

Push mechanisms are intended to reduce the investment needed to research and develop new drugs by distributing the expenditures across multiple parties, thereby encouraging more R&D. Examples of push incentives include increasing access to research, providing research grants, offering tax incentives and establishing public–private partnerships for sharing R&D outlays[28]. Push mechanisms can be implemented at national, regional and international levels. Given the importance of coordinating global R&D activities toward targeting the critical and high-priority pathogens and the most burdensome infections and to avoid duplication of work and maximize impact, there has been a trend toward supporting international initiatives that can implement global strategies to align the antibiotic pipeline with public health need[29].

A synergistic set of international push mechanisms has been deployed, covering all sequential links of the antibiotic innovation chain (Fig. 2). Starting with the earliest stages of translation from academic research to product development, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR; https://www.jpiamr.eu/about/who-we-are/) is an international collaborative platform engaging 29 nations to coordinate national AMR research funding, including funding for antibiotic R&D. The European Commission has announced plans to evolve the JPIAMR into a 7-year One Health AMR Partnership. The early stages of development also benefit from regional or national incubators, such as INCATE (https://www.incate.net/) and PACE (https://www.ukri.org/what-we-do/browse-our-areas-of-investment-and-support/pathways-to-antimicrobial-clinical-efficacy-pace/), which facilitate the translation of research projects between academia and industry.

Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X; https://carb-x.org/) was created in 2016 as a nonprofit, public–private partnership to accelerate the development of priority R&D projects, from hit-to-lead to first-in-human studies. It has raised more than US $900 million from four governments (US, Germany, UK and Canada) and three private foundations (the Wellcome Trust, the Bill & Melinda Gates Foundation and the Novo Nordisk Foundation). CARB-X selects early-stage R&D projects globally submitted via open funding calls and provides awardees with non-dilutive funding and comprehensive scientific, regulatory and business support (Fig. 3).

Since its creation, CARB-X has supported 64 R&D therapeutic projects in eight countries, with notable progress: ten projects have advanced into or completed clinical trials, and five projects remain active in clinical development, including late-stage clinical trials. Additionally, nine product developers with active R&D projects have already secured follow-on funding that can help support clinical development after leaving the CARB-X portfolio. Focusing on similar stages of development to CARB-X, in 2018, Novo Holdings established Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR; https://www.repair-impact-fund.com/) Impact Fund and invested in companies involved in discovery and early-stage development of therapies for drug-resistant infections. The Novo REPAIR fund portfolio comprises 11 companies but has paused investments in additional companies. Showing synergies among push mechanisms, ten companies within the REPAIR fund's portfolio also received support from CARB-X.

The EU Innovative Medicines Initiative New Drugs for Bad Bugs (https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb) supported preclinical development, but no R&D project remains active, and its successor (Innovative Medicines Initiative AMR Accelerator; https://www.imi.europa.eu/projects-results/project-factsheets/amr-accelerator) currently has a limited focus on antibiotic R&D outside tuberculosis. The European Commission is exploring how its new Health Emergency Preparedness and Response Authority can contribute to the global push-and-pull incentive ecosystem after selecting AMR as one of its three priorities[29,30].

In 2016, the Global Antibiotic Research and Development Partnership (GARDP; https://gardp.org/about-gardp/) was created to carry out R&D activities that support and complement commercially driven R&D, with a research portfolio governed by global public health needs, including discovery and exploratory research and clinical development for specific therapeutic areas or populations that are not a commercial priority. GARDP has been funded by nine governments (Australia, Canada, Germany, Japan, Luxembourg, Monaco, the Netherlands, Switzerland and the UK), four foundations (the Bill & Melinda Gates Foundation, the Leo Model Foundation, the Right Foundation and the Wellcome Trust), the non-governmental organization Médecins Sans Frontières and the EU.

https://doi.org/10.1038/s41591-024-03218-w

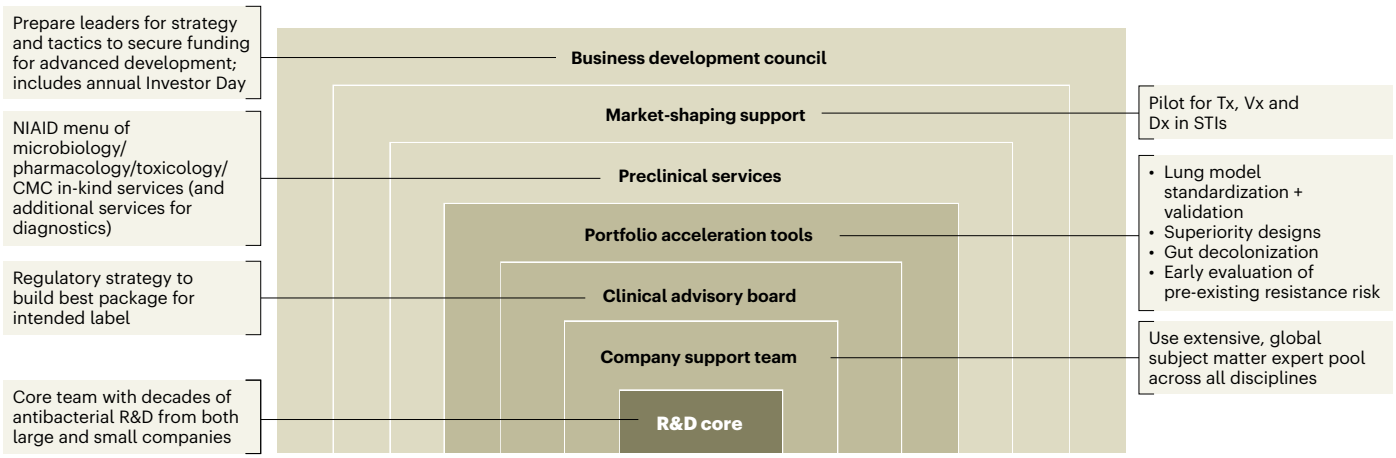

Fig. 3 | CARB-X support model. In addition to non-dilutive funding, CARB-X provides the most promising early-stage projects globally with comprehensive scientific, regulatory and business support. CMC, chemistry, manufacturing and controls; STIs, sexually transmitted infections; Tx, treatments; Vx, vaccines; Dx, diagnostics.

GARDP finances and undertakes R&D activities with its partners, collaborators and service providers and works with partners to complete development of novel compounds and bring these products through regulatory approval. For example, GARDP formed a collaboration agreement with Entasis Therapeutics (subsequently acquired by Innoviva Speciality Therapeutics) to complete the development of zoliflodacin, a new oral antibiotic to treat gonorrhea[31]. This included GARDP sponsoring and leading a pivotal global phase 3 trial, with trial sites in low- and middle-income countries (LMICs), which are often excluded from clinical research[32,33], and leading on the post-phase 2 clinical and pharmaceutical development activities. GARDP estimates that its total costs will amount to approximately €80 million, including support for the phase 3 trial with ~1,000 patients across five countries, as well as clinical pharmacology studies, pharmaceutical development of the final drug product, registration in at least two LMICs and future expansion of the safety database in specific populations.

GARDP also has programs on discovery and exploratory research, serious bacterial infections and children's antibiotics, focusing on infections that affect children and infants, because one in five deaths associated with antibiotic-resistant infections occurs in children under the age of five, with 99.7% of those deaths in LMICs[1]. To develop treatments for neonatal sepsis, GARDP has initiated an international public health trial, NeoSep1, to evaluate potential new combination treatment regimens, with results expected in 2027 (ref. 34).

In 2020, to temporarily bridge the funding gap, 23 pharmaceutical companies, along with the European Investment Bank, the Wellcome Trust, the Boehringer Ingelheim Stiftung and the Novo Nordisk Fonden, committed approximately US $1 billion to the AMR Action Fund (https://www.amractionfund.com/), which supports companies conducting antibiotic clinical development for priority bacterial and fungal pathogens identified by the WHO, the US Centers for Disease Control and Prevention and other national public health entities. In addition to providing investment capital, the AMR Action Fund provides strategic, tactical and technical support to its portfolio companies. Since 2022, the AMR Action Fund has invested in six companies carrying out clinical trials of antibacterials for priority pathogens. The AMR Action Fund has a goal to support two to four approvals of new antimicrobials by 2030, and one of its eight portfolio companies (https://www.amractionfund.com/investments#out-portfolio) gained an approval from the Food and Drug Administration in April 2024, while another has filed a new drug application (NDA) with the Food and Drug Administration.

Combining national programs and contributions to international partnerships, the US government is currently the largest contributor to push incentives, with the National Institutes of Health (NIH) and the National Institute of Allergy and Infectious Diseases (https://www.niaid.nih.gov/research/recent-initiatives-antimicrobial-resistance) focusing mostly on the earliest stages of research and the Biomedical Advanced Research and Development Authority (https://medicalcountermeasures.gov/barda/cbrn/antibacterials/) focusing on the latest stages before and after market approval. The other largest contributors to push incentives globally are the European Commission, German and UK governments (to CARB-X and GARDP) and the Wellcome Trust (to CARB-X; https://dashboard.globalamrhub.org/). Other governments and private foundations have also increased their contributions to support antibiotic R&D[35–37]. According to the Global AMR R&D Hub, which includes public and philanthropic funding, there are 195 active projects across the entire pipeline with a total value of US $559.5 million (Fig. 4 and Table 1). However, according to recent estimates, push mechanisms for antibiotic R&D will require an additional global investment ranging between $250 million and $400 million per year[38].

Pull incentives

In the absence of a sustainable economic market for antibiotics, private capital will be refractory to investing in antimicrobial innovation. Therefore, to facilitate a sustainable innovation ecosystem, policy mechanisms are required to delink revenue from sales volume and reward investment in the successful development of antimicrobials meeting public health needs.

There is consensus across industry and some other stakeholders, including several governments, on the need for pull incentives[30]. To attract the necessary level of private investment, the value of such incentives needs to be sufficient to deliver reasonable returns to investors. Estimates for the amount needed range from US $2 billion to $4 billion[39,40], typically proposed to be paid over a 10-year period. According to some[9,41], this would be adequate to provide an appropriate return on investment in R&D to lead to the approval of one needed new antibiotic. The USA introduced an incentive in 2012 under the Generating Antibiotic Incentives Now (GAIN) Act, providing 5 years of non-patent exclusivity for qualifying antibiotics, but its impact has been limited because the return of investment was insufficient and, in some cases, not targeted to the highest-value novel antibiotics that address unmet medical needs.

Since 2016, the G7 (consisting of Canada, France, Germany, Italy, Japan, the United Kingdom and the United States) has recognized the urgency of public health needs for new antibiotics and has made repeated statements supporting progress for push and pull incentives. While the commitments are welcome and reflect global economic

https://doi.org/10.1038/s41591-024-03218-w

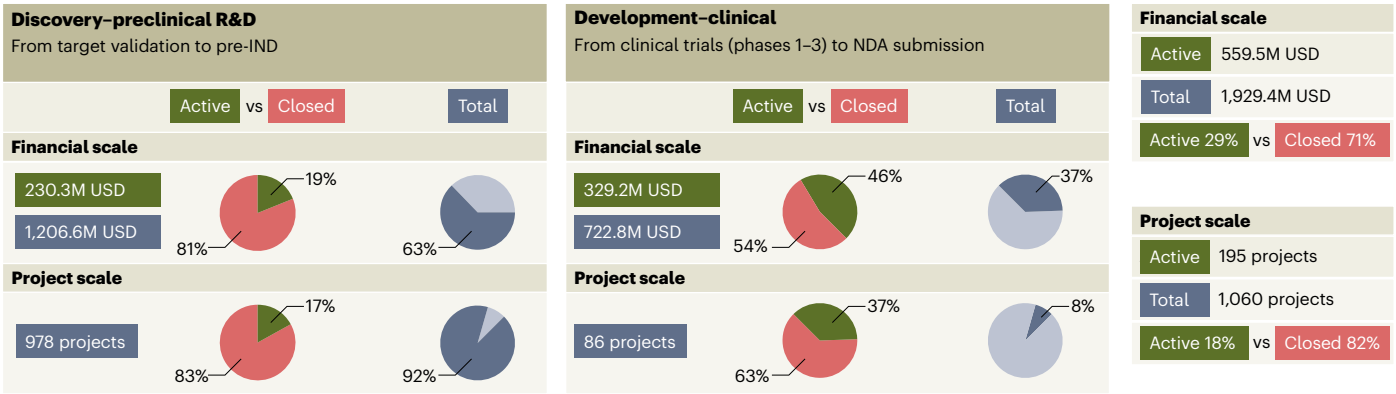

Fig. 4 | Allocation of public and philanthropic investments in R&D of human antibacterial therapeutics globally, by research stage. Data are from the Global AMR R&D Hub's Dynamic Dashboard and cover the period from 1 January 2017 to 14 June 2024. Key to pie chart colors: active projects are shown in green, closed projects are shown in red, and percent total funding and percent total number of projects are shown in blue. Projects targeting human bacterial pathogens (single-sector projects only), excluding *Mycobacterium tuberculosis*, were included in the analysis. Discovery comprises target assessment and validation, hit discovery process and preclinical R&D up to filing an investigational NDA (IND). Development includes the progression of selected candidates from IND to commercialization and concludes with submission of an NDA. Some projects span more than one stage; therefore, investments were split accordingly but not the number of projects. Hence, the total number of projects does not add up. USD, United States Dollars; 'active' indicates projects that were in progress as of 14 June 2024; 'closed' indicates projects completed as of 14 June 2024. The data available from the Dynamic Dashboard are not exhaustive and are subject to limitations and caveats; see https://globalamrhub.org for further information. All values are correct as of 24 July 2024.

Table 1 | Major public and philanthropic funders of antibiotic R&D across the pipeline[a]

Funder	Discovery–IND	Clinical development–NDA
NIH (USA)	41.3%	2.2%
Biomedical Advanced Research and Development Authority (USA)	1.7%	58.7%
CARB-X (global partnership)	23.1%	2.3%
GARDP (global partnership)	0.7%	12.7%
InnovFin (IDFF) (EU)	--	9.5%
Innovative Medicines Initiative (EU)	4.5%	0.5%
Congressionally Directed Medical Research Programs (USA)	2.1%	3.7%
Cystic Fibrosis Foundation (USA)	1.9%	3.9%
Impact Fund (DK)	3.4%	0.7%
European Commission (EU)	2.3%	1.2%
Federal Ministry of Education and Research (DE)	2.4%	0.1%
Innovate UK (UK)	1.7%	0.5%
Defense Threat Reduction Agency (USA)	–	2.8%
Wellcome Trust (UK)	1.6%	–

[a]Data are from the global AMR R&D Hub and cover the period from 1 January 2017 to 14 June 2024, indicating allocation of public and philanthropic investments in R&D of human antibacterial therapeutics globally. Investments made by each selected funder are indicated as a percentage of the total funding volume per research stage. Projects targeting human bacterial pathogens (single-sector projects only), excluding *M. tuberculosis*, were included in the analysis. Data from the Global AMR R&D Hub's Dynamic Dashboard are subject to limitations and caveats; see https://globalamrhub.org for further information. IDFF, Infectious Diseases Finance Facility.

realities, concrete progress on implementation has been limited, despite strong economic and health returns to governments on these investments[42,43].

The UK has launched an innovative pull incentive: a subscription model for purchasing antibiotics that has the dual objective to stimulate investment and to guarantee access for UK patients[44]. This could serve as a model for other countries to consider as a mechanism to incentivize antibiotic R&D. For a predictable and modest annual payment from England's National Health Service to a pharmaceutical company, the UK model is likely to deliver the intended results of guaranteed availability of new antibiotics, regardless of the volume needed. The model includes fixed payments for the developer. These represent a fair share of the global total based on the UK's relative gross domestic product and, according to the UK government, represent a fair contribution it should make to pay for the successful development of a novel antibiotic, via a transparent, pragmatic mechanism to assess the value of each antibiotic and a pathway for engaging manufacturers at an early stage in the contracting process to support their investment decisions. It thereby aims to ensure that the model delivers a win–win for UK taxpayers and the companies involved. The UK completed a successful pilot phase with two innovative antibiotics and is now finalizing the design for longer-term rollout.

Canada has announced plans for a pilot incentive based on the UK model. Progress of the current proposals in the USA (the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act) and the EU, as well as upscaling of a Japanese pilot incentive program (which does not yet incentivize R&D), will be crucial to the overall success and wider adoption of this model[45,46]. The PASTEUR Act has bipartisan support in the US Congress and could deliver between $750 million and $3 billion to an innovating company, although multiple efforts to enact the PASTEUR Act have not yet succeeded. In Europe, proposals include several options that could be complementary, such as a transferable exclusivity voucher (TEV) and guaranteed revenue across member states. The concept is that member states enact pull mechanisms that together trigger the necessary private investment. Success hinges on the biggest markets: if the PASTEUR Act is not enacted and the TEV and alternative European pull incentives fail, the remaining national pull incentives are unlikely to provide a sufficient incentive to the largest pharmaceutical companies to re-enter the field[47]. Modeling suggests that, without the implementation of such incentives, the antibiotic pipeline could further decrease over the next decade, whereas a return to growth, with more approvals, may be seen within a few years after the introduction of effective pull incentives[48].

Although there is no evidence yet of the impact of the UK's subscription mechanism[49,50], it will be important to evaluate its effect in stimulating additional antibiotic R&D, particularly if expanded to other

countries. Currently, the model neither directly requires nor encourages recipients to strengthen access in LMICs. Other pull incentive models, such as the TEV, have raised concerns from multiple EU member states and civil society organizations that they may be too costly for national health budgets and may not be the most effective means to encourage small or large pharmaceutical companies to address AMR[51]. Pull incentives could also be designed to strengthen access in LMICs in a more proactive way.

Making antimicrobials accessible to all who need them

While antimicrobial consumption is arguably the key driver of AMR, a lack of access to needed antibiotics is an increasing problem globally and (counterintuitively) is also a driver of AMR, because inappropriate antibiotic use drives resistance to available drugs. Many countries, including both LMICs (particularly in Africa[52]) and HICs, face a growing crisis of inadequate access and antibiotic shortages[53,54], access barriers are multifaceted, and global availability, affordability and equity must be promoted.

A major challenge is the balance between access to and excess of antimicrobial use. Although overuse of antimicrobials is reported at a population level in many LMICs[55], most vulnerable populations still lack access to essential antimicrobials when needed. Global shortages and inequitable access affect patient safety and health outcomes, increasing morbidity and mortality. One consequence of this access issue is a growing market of substandard and falsified drugs widely available to purchase over the counter in many LMICs, which often lack sufficient regulatory mechanisms for evaluating, approving and monitoring and/or auditing antimicrobials in the market[56]. Global access without clinical oversight via sales through the internet is also an increasing problem in many countries (including HICs)[57], and this is influenced by lack of access to adequate healthcare.

Recently, the Mapping Antimicrobial Resistance and Antimicrobial Use Partnership study observed 0.01% consumption of Reserve antibiotics in six of 14 African countries in the study[58–60], compared to 1% and 0.2% consumption in the United States and Europe[61]. The current landscape of antimicrobial accessibility highlights disproportionate availability of and access to the WHO AWaRe Watch or Reserve antimicrobials in HICs compared to LMICs[55,62]. Recently launched antibiotics are also not widely available across HICs[63]. The lack of sufficient global market demand for several older antibiotics has led to their withdrawal and the introduction of the term 'forgotten antibiotics'; this can be problematic if one is subsequently needed to treat MDR infections, as happened with colistin[64].

To address access, it is important to have strategies that combine R&D and access initiatives, with a focus on partnerships. To facilitate this, it is essential that policymakers and politicians are fully aware of the issues and involved in providing solutions.

Partnering to combine R&D and access initiatives

There remains a need for governments and philanthropies to engage in strategic partnerships with not-for-profit and private sectors to drive sustainable R&D, align public and private interests and facilitate equitable access to antibiotics. When providing financing or incentives, governments and philanthropies should ensure that the resulting antibiotics meet public health needs (as in WHO disease strategies and roadmaps) and are widely accessible[65]. Such partnerships should encourage transparency, knowledge sharing, pre-competitive collaboration, adhering to responsible manufacturing practices and facilitation of availability and affordability[66].

On the basis of the experiences of product development partnerships for poverty-related diseases, risk- and reward-sharing mechanisms such as push and pull mechanisms will be key to incentivizing private sector participation[67]. Governments and philanthropies can share with industry the financial risks associated with antibiotic development, while ensuring that financiers and innovators are appropriately rewarded for successful innovations. This approach should strike a balance between stimulating R&D and ensuring that global public health needs are met[68].

The combined goal of equitable access and antibiotic stewardship should be included in antibiotic R&D financing and incentivizing models. To achieve these objectives, three principles (the three 'As' of availability, affordability and appropriate access) must guide antibiotic development and distribution and delivery processes to ensure that antibiotics are used judiciously on the basis of medical need. The AWaRe classification that aims to reduce consumption of Watch and Reserve antibiotics needs to be more widely adhered to.

Product development should also be approached through an integrated R&D and access approach. This requires that research activities and access considerations are aligned and supported from the outset and consistent with globally coordinated mechanisms. Key aspects include shaping clinical development to cater for real-world needs, optimizing pharmaceutical development to simplify administration and reduce production costs, and generating relevant clinical data and medical evidence to support appropriate use in diverse settings after approval, with the necessary funding to achieve the access goals.

Availability of antibiotics can be enhanced through strategies for ensuring global availability, that is, market approval in all jurisdictions[69]. Companies can either do this directly or through voluntary licensing and agreements with quality manufacturers and distributors, negotiated bilaterally or facilitated by organizations such as GARDP or the Medicines Patent Pool[70]. This can help expedite access to life-saving antibiotics and facilitate more regionally diversified manufacturing capacities, ensuring more resilient supply chains, which are particularly important in crises and emergencies.

Affordability needs to be ensured by early investment in pharmaceutical manufacturing to reduce the marginal cost of production, which benefits all countries, as well as fair pricing practices that link to the relative wealth of a country and are supported by public reimbursement for the most vulnerable populations[71].

Funders and investors can support these principles and policies through contractual conditions between funding entities, SMEs, pharmaceutical companies and nonprofit R&D organizations. Stimulating R&D for antibiotics and ensuring equitable access demand a comprehensive and collaborative approach. Alignment on policies and contractual conditions will facilitate addressing the antibiotic crisis and safeguard public health. Such conditions can be satisfied in part through partnership with third parties, such as GARDP, that can apply an integrated R&D and access approach to enable pharmaceutical partners to meet such obligations.

Public–private partnerships play a crucial role in making new antimicrobials accessible around the world. For example, all CARB-X-funded product developers are contractually obligated to develop stewardship and access plans to facilitate availability of innovative products to patients who need them, as well as responsible use. With key partners in the innovation and access ecosystem (including GARDP), CARB-X produced a Stewardship and Access Plan Development Guide to support developers to produce impactful and comprehensive plans[72]. GARDP has initiated access-related investments for zoliflodacin; this included generating clinical evidence to facilitate appropriate use, reduction of the cost of manufacturing and simplifying the route of administration. In its agreement with Entasis, GARDP secured market access rights for 150 countries, and, if approved, this should improve registration and access of zoliflodacin in these countries[31]. Similarly, not-for-profit partnerships can facilitate access to treatments even when not participating in clinical development. In 2022, GARDP signed a license agreement with Shionogi for the rights to manufacture and commercialize cefiderocol, a treatment for certain

Gram-negative bacterial infections, in 135 countries[73] that historically have limited or no access to new, innovative antibiotics.

Addressing the 'brain drain' in antibiotic R&D

With about 80% of researchers who were active in antibiotic R&D now working in other fields, there is a worrying diminishingly small number of experts in antibiotic R&D. This scientific 'brain drain' further complicates efforts to tackle AMR, as it affects every part of the drug development process, from basic discovery research through clinical testing and beyond[74].

To help rectify this, CARB-X provides grant holders with access to 100+ subject matter experts; many previously worked for large and small product developers that have exited antibiotic R&D. They provide advice on projects within the CARB-X portfolio. CARB-X also manages portfolio acceleration tools to develop a higher-level understanding of common issues faced by the small teams carrying out antibiotic R&D, creating efficiencies across multiple funded product developers. The results of portfolio acceleration tools are also shared publicly to benefit the larger antibiotic R&D community.

GARDP has established the REVIVE (https://revive.gardp.org/) education and outreach program to connect and support the antimicrobial R&D community also with >170 R&D experts. GARDP's program helps to retain and freely share invaluable experience and knowledge crucial for the antibiotic R&D community. Learning and knowledge exchange is provided free of charge globally via various activities, including webinars, resources (for example, Antimicrobial Encyclopaedia) and co-hosting the annual, free virtual Antimicrobial Chemotherapy Conference (https://acc-conference.com/).

Despite these activities, national and international professional societies must better support the antibiotic R&D community.

The role of policymakers and politicians

The High-Level Meeting at the 2024 UN General Assembly (including negotiations of a second Political Declaration on AMR) and the High-Level Ministerial Conference on AMR, which follows soon after, are once more elevating AMR to the global stage, having been displaced due to the coronavirus pandemic and subsequent discussions on pandemic preparedness.

Governments could explore the value of an international agreement to address AMR as for other translational challenges, such as climate change, desertification and biodiversity loss. International cooperation to address AMR is an endeavor across four international agencies: the Food and Agriculture Organization of the United Nations, the UN Environment Programme, the WHO and the World Organisation for Animal Health (the Quadripartite). The World Health Assembly and the G7 (ref. 75) and G20 + 1 (African Union)[76] have also made commitments to strengthen R&D and access to antibiotics. To help the many governments who have not fully implemented these commitments or their national action plans[77,78], policymakers must implement an appropriate framework of targets and monitoring mechanisms to enable international cooperation.

An international framework will not be generated through any of the currently foreseen pandemic instruments. Even though AMR is a pandemic of drug-resistant infections, pandemic instruments under negotiation either exclude antibiotic resistance or do not address AMR with the specificity required to govern a complex ecosystem of public, not-for-profit and private actors[79]. Thus, politicians and policymakers must devise a new framework on AMR to finance the end-to-end development of, manufacturing of, approval of and access to new treatments. Regional technical cooperation and political alignment, such as that in the EU[80], the ASEAN (https://asean.org/) or the African Union[81], are an important step in the right direction[82,83]. In addition, there is a need for continued voluntary and pragmatic coalitions and partnerships of countries and foundations that can ensure progress on the global scene and motivate others to join or align.

Some governments already deserve credit for establishing entities such as the Global AMR R&D Hub and the JPIAMR, and for funding organizations such as GARDP and CARB-X, as well as a national-level pull incentive, such as the UK's subscription mechanism. However, these commitments must be universally applied, adequately funded, binding, routine, global, predictable, sustainable and long term. As part of their responsibility to address AMR, governments should commit to additional investments in R&D according to their capacity and needs. In addition, governments should create appropriate public–private mechanisms for developing, manufacturing and the distribution of antibiotics.

Finally, politicians and policymakers should strengthen and expand existing programs and entities that facilitate and perform R&D and promote equitable access to new and existing antibiotics. There is an opportunity to proactively identify institutions and mechanisms that can play a critical role in ensuring equitable access. This includes recognition of the global priorities set by the WHO Prequalification Programme to validate quality-assured antibiotics and support for SECURE (https://www.secureantibiotics.org/), a new initiative sponsored by the WHO and GARDP, to expand access to essential antibiotics.

The WHO also has an important role to play in research priority setting through a combination of the priority pathogens list, research agendas that identify the most urgent research problems that need to be addressed[84], and target product profiles[85] that provide clear guidance to drug developers. Additionally, all involved stakeholders need to work together to identify globally relevant R&D targets that can support push and pull instruments delivering new antibiotics and treatment regimens that respond to the most urgent unmet medical needs globally.

Conclusion

Now is the time to raise the urgency, ambition and commitments of the world's leaders to fully support a new antibiotic R&D ecosystem that is grounded by effective push and pull mechanisms that incentivize the nonprofit and private sectors to conduct global public health-driven antibiotic R&D. Success will require a coordinated effort among countries, led by an independent expert panel (similar to efforts on climate change), to lead and guide pharmaceutical companies, SMEs, nonprofit global organizations, the healthcare community and civil society organizations to ultimately reduce global infection-associated morbidity and mortality.

References

1. Murray, C. J. L. et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* **399**, 629–655 (2022).
2. AMR Leaders. Towards specific commitments and action in the response to antimicrobial resistance. *Global Leaders Group on Antimicrobial Resistance* https://www.amrleaders.org/resources/m/item/glg-report (4 April 2024).
3. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. *World Health Organization* https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed (27 February 2017).
4. World Health Organization. WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. *World Health Organization* https://www.who.int/publications/i/item/9789240093461 (17 May 2024).
5. Silver, L. L. A Gestalt approach to Gram-negative entry. *Bioorg. Med. Chem.* **24**, 6379–6389 (2016).
6. Sundqvist, M. Reversibility of antibiotic resistance. *Ups. J. Med. Sci.* **119**, 142–148 (2014).

7. World Health Organization. 2023 antibacterial agents in clinical and preclinical development: an overview and analysis. *World Health Organization* https://www.who.int/publications/i/item/9789240094000 (14 June 2024).
8. O' Neill, J. et al. AMR Review. May 19, 2016 — Tackling drug-resistant infections globally: final report and recommendations. *Review on Antimicrobial Resistance* https://amr-review.org/Publications.html (19 May 2016).
9. Drive-AB Consortium. DRIVE-AB outputs: reports and briefing. *Drive AB* https://drive-ab.eu/drive-ab-outputs/drive-ab-reports/ (2016).
10. Stern, S. et al. Breaking through the wall: a call for concerted action on antibiotics research and development. *Boston Consulting Group* https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf (February, 2017).
11. Anderson, M., Panteli, D. & Mossialos, E. Policy Brief 51: How can the EU support sustainable innovation and access to effective antibiotics? policy options for existing and new medicines. *European Observatory on Health Systems and Policies* https://eurohealthobservatory.who.int/publications/i/how-can-the-eu-support-sustainable-innovation-and-access-to-effective-antibiotics-policy-options-for-existing-and-new-medicines (21 June 2023).
12. Turnidge, J. & Christiansen, K. Antibiotic use and resistance—proving the obvious. *Lancet* **365**, 548–549 (2005).
13. World Health Organization. 2021 AWaRe classification. WHO access, watch, reserve, classification of antibiotics for evaluation and monitoring of use. *World Health Organization* https://www.who.int/publications/i/item/2021-aware-classification (30 September 2021).
14. European Centre for Disease Prevention and Control. Antimicrobial resistance targets: how can we reach them by 2030? *ECDC* https://www.ecdc.europa.eu/sites/default/files/documents/amr-brief-eaad-2023-update.pdf (2023).
15. World Health Organization. Lack of innovation set to undermine antibiotic performance and health gains. *World Health Organization* https://www.who.int/news/item/22-06-2022-22-06-2022-lack-of-innovation-set-to-undermine-antibiotic-performance-and-health-gains (22 June 2022).
16. Magnano San, L. R. et al. How antimicrobial resistance is linked to climate change: an overview of two intertwined global challenges. *Int. J. Environ. Res. Public Health* **20**, 1681 (2023).
17. Dolecek, C., Shakoor, S., Basnyat, B., Okwor, T. & Sartorius, B. Drug-resistant bacterial infections: we need urgent action and investment that focus on the weakest link. *PLoS Biol.* **20**, e3001903 (2022).
18. World Health Organization. Immunization coverage. *World Health Organization* https://www.who.int/news-room/fact-sheets/detail/immunization-coverage (15 July 2024).
19. Chimhini, G., Magwenzi, M. & Fitzgerald, F. C. Infection prevention and control in low-resource settings: the need for the local, the contextual and the pragmatic. *Infect. Prev. Pract.* **4**, 100135 (2022).
20. Nour, S., Stokle, E., Ashiru-Oredope, D. & Wesangulae, E. Challenges of implementing antimicrobial stewardship tools in low to middle income countries (LMICs). *Infect. Prev. Pract.* **5**, 100315 (2023).
21. Aminov, R. A brief history of the antibiotic era: lessons learned and challenges for the future. *Front. Microbiol.* **1**, 134 (2010).
22. Outterson, K. et al. Patient access in 14 high-income countries to new antibacterials approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010–2020. *Clin. Infect. Dis.* **74**, 1183–1190 (2022).
23. World Health Organization. 2021 antibacterial agents in clinical and preclinical development: an overview and analysis. *World Health Organization* https://www.who.int/publications/i/item/9789240047655 (27 May 2022).
24. Antibiotics: the economics must support the science. *Nature* **625**, 7 (2024).
25. Thomas, D. & Wessel, C. The state of innovation in antibacterial therapeutics. *Biotechnology Innovation Organization* https://www.bio.org/sites/default/files/2022-02/The-State-of-Innovation-in-Antibacterial-Therapeutics.pdf (February, 2022).
26. Strich, J. et al. Assessing clinician utilization of next-generation antibiotics against resistant Gram-negative infections in U.S. hospitals: a retrospective cohort study. *Ann. Intern. Med.* **177**, 559–572 (2024).
27. Thomas, D. & Wessel, C. The state of innovation in antibacterial therapeutics. *Biotechnology Innovation Organization* https://www.bio.org/sites/default/files/2022-04/BIO-Antibacterial-Report-2022.pdf (February 2022).
28. Renwick, M. J., Brogan, D. M. & Mossialos, E. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *J. Antibiot.* **69**, 73–88 (2016).
29. Health Emergency Preparedness and Response Authority. Research and development of medical countermeasures. *European Commission* https://health.ec.europa.eu/health-emergency-preparedness-and-response-hera/preparedness/research-and-development-medical-countermeasures_en (2024).
30. European Commission. Pre-draft proposal for a European partnership under Horizon Europe One Health Antimicrobial Resistance. *European Commission* https://research-and-innovation.ec.europa.eu/system/files/2022-02/ec_rtd_he-partnerships-onehealth-amr.pdf (9 February 2022).
31. Global Antibiotic Research and Development Partnership. Entasis Therapeutics and the Global Antibiotic Research & Development Partnership to develop a new treatment for gonorrhea. *GARDP* https://gardp.org/entasis-therapeutics-and-the-global-antibiotic-research-development-partnership-to-develop-a-new-treatment-for-gonorrhea/ (6 July 2017).
32. Atal, I., Trinquart, L., Porcher, R. & Ravaud, P. Differential globalization of industry- and non-industry-sponsored clinical trials. *PLoS ONE* **10**, e0145122 (2015).
33. World Health Organization. Number of clinical trial registrations by location, disease, phase of development, age and sex of trial participants (1999–2022). *World Health Organization* https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-trial-registrations-by-year-location-disease-and-phase-of-development (February 2023).
34. Global Antibiotic Research and Development Partnership. NeoSept1: a study to determine the ranking of existing and new antibiotics combinations to treat newborn babies who are in hospital with severe sepsis. *ISRCTN registry* https://www.isrctn.com/ISRCTN48721236 (17 January 2022).
35. Public Health Agency of Canada. Government of Canada makes important investment to fight antimicrobial resistance (AMR), *Government of Canada* https://www.canada.ca/en/public-health/news/2023/05/government-of-canada-makes-important-investment-to-fight-antimicrobial-resistance-amr.html (11 May 2023).
36. Global Antibiotic Research and Development Partnership. Japan government funding supports GARDP's efforts to counter antibiotic resistance. *GARDP* https://gardp.org/japan-government-funding-supports-gardps-efforts-to-counter-antibiotic-resistance/ (19 October 2023).

37. Novo Nordisk Foundation. Novo Nordisk Foundation partners with CARB-X to fight drug-resistant infections. *novo nordisk foundation* https://novonordiskfonden.dk/en/news/novo-nordisk-foundation-partners-with-carb-x-to-fight-drug-resistant-infections/ (9 January 2024).
38. European Commission: European Health and Digital Executive Agency. Study on bringing AMR medical countermeasures to the market. *Publications Office of the European Union* https://op.europa.eu/en/publication-detail/-/publication/51b2c82c-c21b-11ed-8912-01aa75ed71a1/language-en (2023).
39. Outterson, K. Estimating the appropriate size of global pull incentives for antibacterial medicines. *Health Aff.* **40**, 1758–1765 (2021).
40. Evans, E. J., Meyer, A. & Conti, R. M. Sizing a market entry reward for the development of new antibiotics. *Harvard Kennedy School* https://www.hks.harvard.edu/sites/default/files/centers/mrcbg/Final_AWP_232.pdf (May 2024).
41. Morel, C. M. et al. Industry incentives and antibiotic resistance: an introduction to the antibiotic susceptibility bonus. *J. Antibiot.* **73**, 421–428 (2020).
42. Bonnifield, R. & Towse, A. An ambitious USG advanced commitment for subscription-based purchasing of novel antimicrobials and its expected return on investment. *Center for Global Development* https://www.cgdev.org/publication/ambitious-usg-advanced-commitment-subscription-based-purchasing-novel-antimicrobials (15 November 2022).
43. Towse, A. & Silverman Bonnifield, R. G7 investments in new antibiotics would pay off — for everyone. *Office of Health Economics* https://www.ohe.org/insight/g7-investments-in-new-antibiotics-would-pay-off-for-everyone/ (9 December 2022).
44. NHS England. NHS steps up battle against life-threatening infections following successful world-first pilot. *NHS England* https://www.england.nhs.uk/2023/07/nhs-steps-up-battle-against-life-threatening-infections-following-successful-world-first-pilot/ (11 July 2023).
45. US Congress. S.1355 — PASTEUR Act of 2023. *congress.gov* www.congress.gov/bill/118th-congress/senate-bill/1355#:~:text=This%20bill%20authorizes%20the%20Department,and%20contains%20other%20related%20provisions (27 April 2023).
46. European Commission. Reform of the EU pharmaceutical legalisation. *European Commission* https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en (26 April 2023).
47. Gotham, D. et al. Reimbursement models to tackle market failures for antimicrobials: approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy* **125**, 296–306 (2020).
48. International Federation of Pharmaceutical Manufacturers and Associations. From resistance to resilience: what could the future antibiotic pipeline look like? *IFMPA* https://www.ifpma.org/publications/from-resistance-to-resilience-what-could-the-future-antibiotic-pipeline-look-like/ (14 May 2024).
49. Global AMR R&D Hub & World Health Organization. Incentivising the development of new antibacterial treatments: 2023 progress report by the Global AMR R&D Hub and WHO. *Global AMR R&D Hub* https://globalamrhub.org/publications/incentivising-the-development-of-new-antibacterial-treatments-2023/ (2023).
50. Glover, R. E., Singer, A., Roberts, A. P. & Kirchhelle, C. Why is the UK subscription model for antibiotics considered successful? *Lancet Microbe* **4**, e852–e853 (2023).
51. Non-paper — novel stimuli for the development and keeping on the market of antimicrobials. *Politico* https://www.politico.eu/wp-content/uploads/2022/12/01/Non-paper-Transferable-exclusivity-voucher-for-AMR-2.pdf (2022).
52. Liu, L. et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* **385**, 430–440 (2015).
53. Quadri, F. et al. Antibacterial drug shortages from 2001 to 2013: implications for clinical practice. *Clin. Infect. Dis.* **60**, 1737–1742 (2015).
54. Benhabib, A. et al. The French reporting system for drug shortages: description and trends from 2012 to 2018: an observational retrospective study. *BMJ Open* **10**, e034033 (2020).
55. Klein, E. Y. et al. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: an analysis of pharmaceutical sales data. *Lancet Infect. Dis.* **21**, 107–115 (2021).
56. Pyzik, O. Z. & Abubakar, I. Fighting the fakes: tackling substandard and falsified medicines. *Nat. Rev. Dis. Primers* **8**, 55 (2022).
57. Hayhoe, B., Greenfield, G. & Majeed, A. Is it getting easier to obtain antibiotics in the UK? *Br. J. Gen. Pract.* **69**, 54–55 (2019).
58. African Society for Laboratory Medicine. Policy brief and infographics on antimicrobial resistance (AMR) in Africa. *ASLM* https://aslm.org/resource/policy-brief-and-infographics-on-antimicrobial-resistance-amr-in-africa/ (14 September 2022).
59. Kanu, J. S. et al. National antibiotic consumption for human use in Sierra Leone (2017–2019): a cross-sectional study. *Trop. Med. Infect. Dis.* **6**, 77 (2021).
60. Namugambe, J. S. et al. National antimicrobial consumption: analysis of central warehouses supplies to in-patient care health facilities from 2017 to 2019 in Uganda. *Trop. Med. Infect. Dis.* **6**, 83 (2021).
61. Robertson, J. et al. Variations in the consumption of antimicrobial medicines in the European region, 2014–2018: findings and implications from ESAC-Net and WHO Europe. *Front. Pharmacol.* **12**, 639207 (2021).
62. Shukar, S. et al. Drug shortage: causes, impact, and mitigation strategies. *Front. Pharmacol.* **12**, 693426 (2021).
63. Outterson, K., Orubu, E. S. F., Rex, J., Årdal, C. & Zaman, M. H. Patient access in 14 high-income countries to new antibacterials approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010–2020. *Clin. Infect. Dis.* **74**, 1183–1190 (2021).
64. Pulcini, C. et al. Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia. *Int. J. Antimicrob. Agents* **49**, 98–101 (2017).
65. Rottingen, J. A. & Farrar, J. Targeted health innovation for global health. *Br. Med. J.* **366**, 15601 (2019).
66. AMR Industry Alliance. The 2023 AMR Industry Alliance progress survey: manufacturing and the environment. *amr Industry Alliance* https://www.amrindustryalliance.org/wp-content/uploads/2023/12/AMRIA_Manufacturing-and-the-environment-FINAL.pdf (2023).
67. Munoz, V., Visentin, F., Foray, D. & Gaule, P. Can medical products be developed on a non-profit basis? Exploring product development partnerships for neglected diseases. *Sci. Public Policy* **42**, 315–338 (2015).
68. Swaminathan, S. et al. Reboot biomedical R&D in the global public interest. *Nature* **602**, 207–210 (2022).
69. Africa Centres for Disease Control and Prevention. Africa CDC spearheads bold move to secure Africa's health future by creating a 50 billion dollar medical market. *AfricaCDC* https://africacdc.org/news-item/africa-cdc-spearheads-bold-move-to-secure-africas-health-future-by-creating-a-50-billion-dollar-medical-market/ (19 February 2024).
70. Gore, C., Morin, S., Røttingen, J. A. & Kieny, M. P. Negotiating public-health intellectual property licensing agreements to increase access to health technologies: an insider's story. *BMJ Glob. Health* **8**, e012964 (2023).

71. Suleman, F., Low, M., Moon, S. & Morgan, S. G. New business models for research and development with affordability requirements are needed to achieve fair pricing of medicines. *Br. Med. J.* **368**, l4408 (2020).
72. Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator. Stewardship and access. *CARB-X* https://carb-x.org/about/stewardship-and-access/ (2024).
73. Global Antibiotic Research and Development Partnership. Shinogi, GARDP and CHAI announce landmark license and collaboration agreements to treat bacterial infections by expanding access to cefiderocol in 135 countries. *GARDP* https://gardp.org/shionogi-gardp-and-chai-announce-landmark-license-and-collaboration-agreements-to-treat-bacterial-infections-by-expanding-access-to-cefiderocol-in-135-countries/ (15 June 2022).
74. AMR Industry Alliance. Leaving the lab: tracking the decline in AMR R&D professionals. *amr Industry Alliance* https://www.amrindustryalliance.org/wp-content/uploads/2023/02/Leaving-the-Lab_final-1.pdf (February, 2024).
75. G7 Health Ministers. G7 Health Ministers' Communiqué. *G7 Germany* www.g7germany.de/resource/blob/974430/2042058/5651daa321517b089cdccfaffd1e37a1/2022-05-20-g7-health-ministers-communique-data.pdf (20 May 2022).
76. G20. G20 call to action on antimicrobial resistance. *G7G20 Documents Database* https://g7g20-documents.org/database/document/2022-g20-indonesia-sherpa-track-health-ministers-ministers-annex-g20-call-to-action-on-antimicrobial-resistance (28 October 2022).
77. Global Coalition on Aging & Infectious Diseases Society of America. 2024 AMR preparedness index progress report. Measuring government action on AMR policy. *Global Coalition on Aging* https://globalcoalitiononaging.com/wp-content/uploads/2024/01/2024-AMR-Index-Progress-Report.pdf (2024).
78. Food and Agriculture Organization of the United Nations, United Nations Environment Programme, World Health Organization &. World Organisation for Animal Health. Global database for tracking antimicrobial resistance (AMR): country self-assessment survey (TrACSS). *WHO* https://amrcountryprogress.org/#/map-viewindicator2.3 (2023).
79. Van Katwyk, S. R. & Outterson K. Introduction: AMR belongs in the pandemic instrument. *Boston University School of Law* https://scholarship.law.bu.edu/cgi/viewcontent.cgi?article=4412&context=faculty_scholarship (2022).
80. Directorate-General for Health and Food Safety. Council recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach. *European Commission* https://health.ec.europa.eu/publications/council-recommendation-stepping-eu-actions-combat-antimicrobial-resistance-one-health-approach_en (13 June 2023).
81. African Union. Africa common position on antimicrobial resistance. *African Union* https://au.int/sites/default/files/newsevents/workingdocuments/36768-wd-sa24481_e_original_africa_common_position_on_antimicrobial_resistance.pdf (2019).
82. ASEAN Health Ministers. ASEAN strategic framework to combat antimicrobial resistance through One Health approach (2019–2030). *ASEAN* https://asean.org/wp-content/uploads/2021/10/Agd-6.2.b_ASEAN-Strategic-Framework-to-Combat-AMR_Adopted-by-AHMM.pdf (2021).
83. Africa Centres for Disease Control and Prevention. African Union framework for antimicrobial resistance control 2020–2025. *Africa CDC* https://africacdc.org/download/african-union-framework-for-antimicrobial-resistance-control-2020-2025 (19 March 2021).
84. World Health Organization. Global research agenda for antimicrobial resistance in human health. *World Health Organization* https://www.who.int/publications/m/item/global-research-agenda-for-antimicrobial-resistance-in-human-health (22 June 2023).
85. World Health Organization. Target product profiles for needed antibacterial agents: enteric fever, gonorrhea, neonatal sepsis, urinary tract infections and meeting report. *World Health Organization* https://www.who.int/publications/i/item/9789240003897 (19 May 2020).
86. Magiorakos, A. P. et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin. Microbiol. Infect.* **18**, 268–281 (2012).
87. Kadri, S. S. et al. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. *Clin. Infect. Dis.* **67**, 1803–1814 (2018).

Acknowledgements

We thank D. Graham-Rowe, R. Malpani, N. Ndembi, L. Srot, C. Sweeney, A.-M. Nia and D. Patel for helping to prepare this Review. We thank L. Ogilvie (Global AMR R&D Hub) for generating Fig. 4 and giving permission for its use in this Review. CARB-X is supported by federal funds from the US Department of Health and Human Services, the Administration for Strategic Preparedness and Response, the Biomedical Advanced Research and Development Authority under agreement number 75A50122C00028 and by awards from Wellcome (WT224842), Germany's Federal Ministry of Education and Research (BMBF), the UK Department of Health and Social Care as part of the Global Antimicrobial Resistance Innovation Fund, the Public Health Agency of Canada, the Bill & Melinda Gates Foundation and the Novo Nordisk Foundation. The US National Institute of Allergy and Infectious Diseases, part of the NIH in Health and Human Services, provides support in the form of in-kind services through access to a suite of preclinical services for product development. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any CARB-X funders. The GARDP is supported by the governments of Canada, Germany, Japan, Monaco, the Netherlands, South Africa, Switzerland, the United Kingdom, the Canton of Geneva and the European Union, as well as Global Health EDCTP3, the RIGHT Foundation and the Wellcome Trust. The GARDP was created by the WHO and the Drugs for Neglected Diseases Initiative in 2016 and was legally registered as the GARDP Foundation in Geneva, Switzerland in 2018. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any GARDP funders. The following companies invest in the AMR Action Fund: Almirall, Amgen, Bayer, Boehringer Ingelheim, Chugai (Roche Group), Daiichi Sankyo, Eisai, Lilly, Boehringer Ingelheim Stiftung, Pfizer, Johnson & Johnson, Lundbeck, the European Investment Bank, GSK, Leo, the Menarini Group, Merck, Novartis, the Novo Nordisk Fonden, Shionogi, Novo Nordisk, Roche, Takeda and UCB. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any AMR Action Fund investors. C.E.M. receives funding from the Wellcome Trust (grant number 222051/Z/20/Z) for her research. J.A. is employed by the IFPMA, which represents the pharmaceutical industry. The content of this Review is solely the responsibility of the authors and does not necessarily represent the official views of the IFPMA, their funders, employers or members.

Competing interests

The authors declare no competing interests. J.A. owns shares in GSK.

Additional information

Correspondence and requests for materials should be addressed to Laura J. V. Piddock.

Peer review information *Nature Medicine* thanks Li Yang Hsu and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Karen O'Leary, in collaboration with the *Nature Medicine* team.