ASPE ASSISTANT SECRETARY FOR PLANNING AND EVALUATION | OFFICE OF SCIENCE AND DATA POLICY

ISSUE BRIEF

November 2024

Novel Antimicrobial Drug Development and Access: U.S. Government Support and Opportunities

Casey Sullivan, Cody R. Fisher, & Julia Taenzer

The U.S. Government supports the pipeline for antimicrobial drugs from basic research to improved use and access, but additional options for support are needed.

KEY POINTS

- The pipeline and commercial market for novel antimicrobial drugs is insufficient to address current and future patient needs or mitigate the loss of effective treatments as antimicrobial resistance spreads.
- The U.S. Government implements a range of efforts to ensure sustainable availability of antimicrobial treatments, supporting research, product development, and appropriate use.
- Opportunities remain to expand appropriate access to antimicrobial drugs domestically and globally and support the sustainable development of antimicrobial drugs into the future, despite the evolution of antimicrobial resistance.

Background

Despite recent progress in the United States and abroad, antimicrobial resistance (AMR) remains a leading cause of disease and death worldwide. In 2021, there were an estimated 4.71 million global deaths associated with, and 1.14 million deaths directly attributed to, bacterial AMR.[1-3] Forecasting predicts over 8 million global deaths associated with, and almost 2 million deaths directly attributed to, bacterial AMR in 2050.[3] In the U.S., at least 2.8 million antibiotic-resistant infections occur and at least 35,000 people die as a result each year.[1] Hospital-onset resistant infections and resulting deaths increased at least 15 percent during the first year of the COVID-19 pandemic, due to longer stays for hospitalized patients and weakened infection prevention and control (IPC) practices in U.S. healthcare facilities.[4] While AMR rates have begun to stabilize, they largely remain elevated from pre-pandemic levels.[5] In addition to the health burden, AMR causes economic burden by increasing the annual cost of health care by USD $66 billion globally.[6] In the U.S., treatment of resistant infections cost an estimated USD $4.6 billion in 2017.[7] Drug-resistant fungal pathogens and infections are also an increasing global public health concern.[8]

To address this threat and preserve the effectiveness of current antimicrobial (AM) drugs, global governments[9-11] and non-governmental stakeholders[12] are working to improve AM drug use and to detect, contain, and reduce the spread of resistant pathogens across the One Health spectrum that recognizes the relationships among the health of humans, animals, plants, and the environment. However, the fight against AMR requires that novel AM drugs are also developed and made accessible. This issue brief focuses on U.S. Government efforts to support the development of and sustainable access to new and innovative AM drugs under the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB).[10,13]

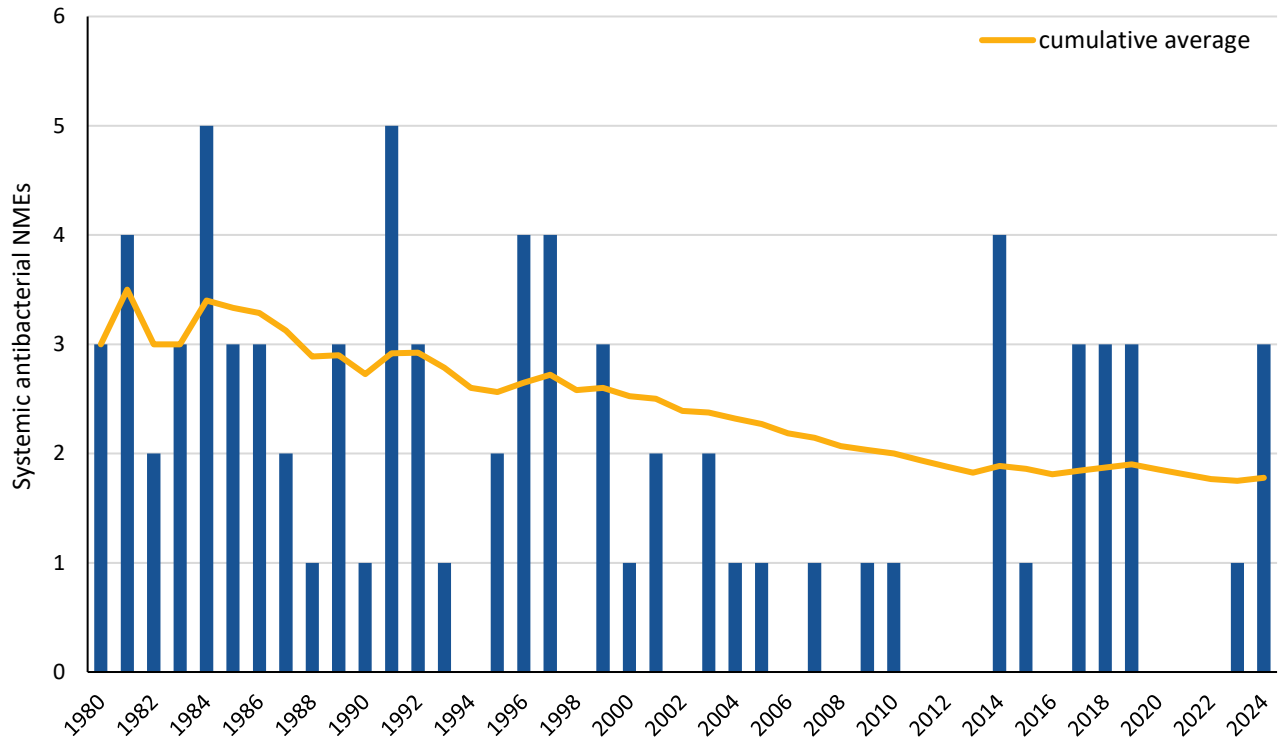
Antimicrobial Drug Pipeline

A continuous pipeline of novel AM drugs is necessary because evolution will inevitably drive the development of pathogens that are resistant to existing AM drugs. The current burden of AMR includes patients who are presently suffering from difficult-to-treat or untreatable infections, who need alternative treatments from those currently available. However, recent reports indicate that the current AM drug pipeline is at significant risk of falling short of current and future healthcare needs.[9,14-17]

Pre-approval products. According to a World Health Organization (WHO) 2023 report, the clinical antibacterial pipeline contained 97 traditional or non-traditional* antibacterial agents and/or combinations that include at least one new therapeutic entity. Of the 32 traditional antibiotics within the pipeline targeting WHO priority pathogens (excluding *M. tuberculosis*), almost half are of a single mechanistic class (β-lactams) with established resistance mechanisms,[14,15] only 12 meet at least one of the WHO's innovation criteria, and only two meet all four criteria (new class, mechanism of action, or target, and absence of cross-resistance).[18]

Recently-approved products. Between June 1980 and October 2024, the U.S. Food and Drug Administration (FDA) approved 80 systemic antibacterial new molecular entities (NMEs; see Figure 1), with 52 approved before 2000 and only four approved between 2020 and 2024.

Figure 1. Number of systemic antibacterial new molecular entities approved by FDA, by year



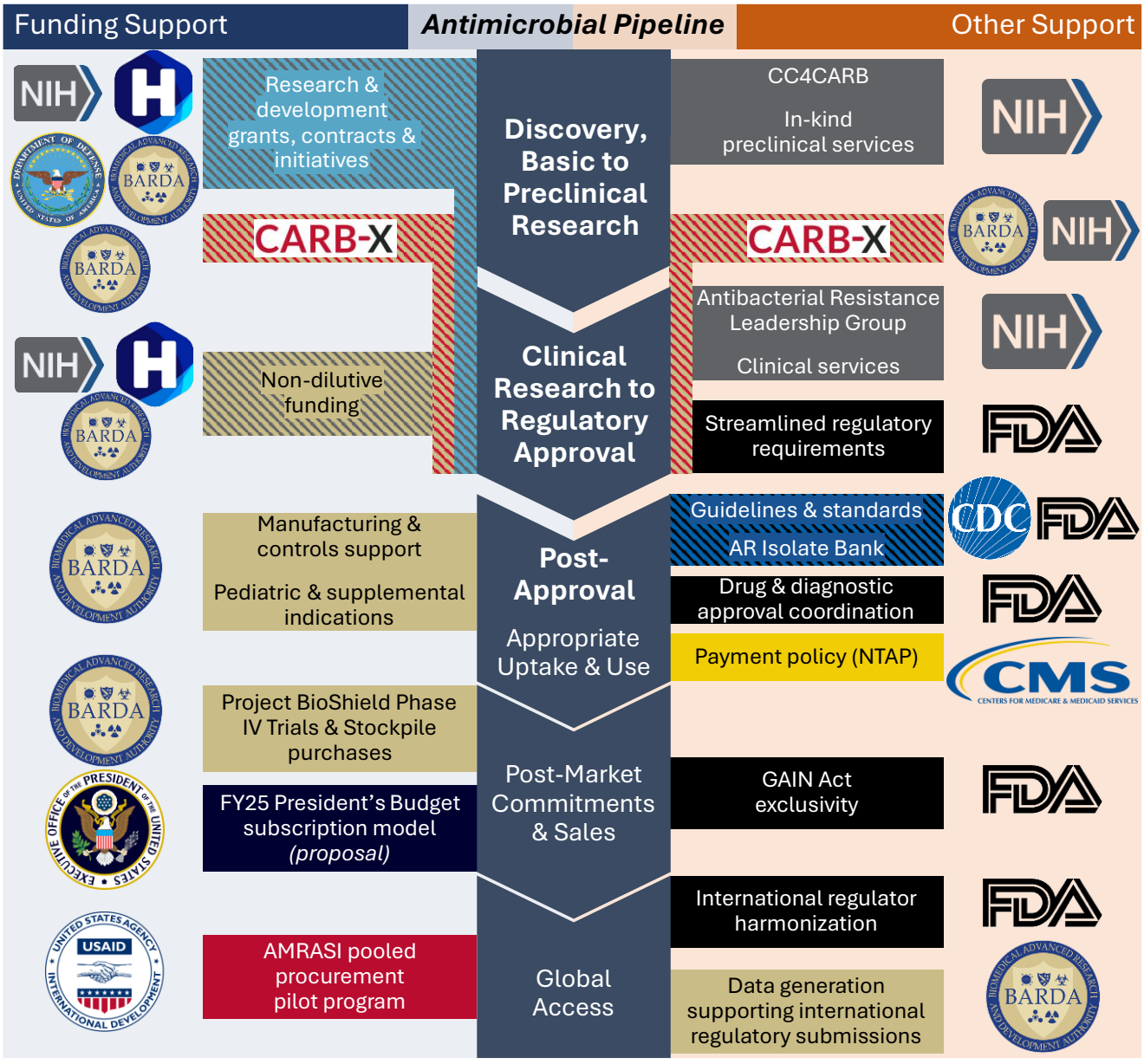
Note: Systemic antibacterial drug NME approvals, inclusive of novel β-Lactamase inhibitors (BLIs) intended for use in combination with a previously approved β-lactam antibacterial drug; excluded are locally acting drugs, drugs to treat invasive fungal infections, drugs narrowly targeted to treat mycobacterial infections such as tuberculosis, *Clostridium difficile*–associated disease, *Helicobacter pylori* eradication, and drugs solely developed to address biothreats such as anthrax or plague; these criteria match Dheman et al., 2021. New molecular entities are typically products that contain active moieties, or core molecules or ions of a drug, that FDA has not previously approved (see https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda).

* Traditional products are direct-acting small molecules, and non-traditional products include bacteriophages, antibodies, anti-virulence agents, immune-modulating agents, microbiome-modulating agents.

U.S. Government Support for Sustainable AM Drug Availability

Developing any pharmaceutical product is an expensive and technically difficult endeavor. However, analyses by the U.S. Department of Health and Human Services (HHS) and other stakeholders find that maintaining sustainable development of and subsequent access to AM drugs involves unique and acute challenges.[16] Figure 2 illustrates U.S. Government support for AM drug development and access at each stage of the pipeline through both funding and other support, such as technical expertise and regulatory guidance. These efforts, also described below, support Goal 4 of the National Action Plan for CARB, which calls for federal agencies to "Accelerate Basic and Applied Research and Development for New Classes of Antibiotics, Other Therapeutics, and Vaccines".[10]

Figure 2. Overview of U.S. Government actions to support sustainable AM drug availability



Discovery, Basic, and Preclinical Research

The science of AM drug discovery and development is challenging.

As noted above, very few AM candidates in the pipeline are considered innovative. This is also true for many newly approved AM drugs approved in recent years; several products are from the same classes and use the same mechanisms of action as established products, and relatively few address priority pathogens. Identifying antibiotic candidates has typically required extensive and time-consuming manual screening and testing of molecular compounds.[19] Once a promising candidate was identified, efforts to move from patent filing to first-in-human testing for recently-approved AM drugs took an average of five years and cost USD $1.2 billion when accounting for the cost of failures and opportunity cost of capital.[20]

U.S. Government efforts

U.S. Government support is a keystone to the scientific enterprise of AM drug discovery. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), supports basic, translational, and clinical research to advance the prevention, diagnosis, and treatment of antimicrobial-resistant infections. In recent years, NIH funding has accounted for an estimated 40 percent of the total global funding from public and philanthropic sources for early-phase AM drug discovery and development.[9] This includes support for discovery to early development research on mechanisms of resistance and discovery of novel and non-traditional treatment strategies. NIH/NIAID supports cutting edge technologies like structural biology, computational modeling, and artificial intelligence to accelerate early discovery through the Bioinformatics Resource Centers (BRCs) for Infectious Diseases and Centers for Research on Structural Biology of Infectious Diseases (CRSTAL-ID). In addition, NIH/NIAID aims to help fill the gap of antibiotic discovery through the Chemistry Center for Combating Antibiotic-Resistant Bacteria (CC4CARB)[21], which focuses on the synthesis, acquisition, and distribution of rationally designed, focused libraries free-of-charge to the global scientific community for use in Gram-negative antibacterial drug discovery programs. NIH/NIAID also provides preclinical and clinical services to product developers at no cost, including *in vitro* and *in vivo* studies and pharmacokinetic and toxicology evaluation, the development of new animal models, and Phase I clinical trials. NIH/NIAID's Omnibus Broad Agency Announcement product development contract provides support for vaccines and therapeutic development from lead optimization through Phase 1 clinical trials and small Phase 2 clinical trials.

The Center for the Biomedical Advanced Research and Development Authority (BARDA), within the HHS Administration for Strategic Preparedness and Response (ASPR), accelerates the development and availability of effective medical countermeasures against multidrug-resistant infections. Since 2010, ASPR/BARDA has provided more than USD $2.4 billion to support the development of more than 160 therapeutics, preventatives, and diagnostics, making it the leading global funder of clinical development of antimicrobial candidates.[22] ASPR/BARDA's support has led to FDA approval of four novel antibiotics and FDA 510(k) clearance of eight AMR diagnostic devices.[22] To address the emerging threat of drug-resistant fungal threats, ASPR/BARDA supported its first program to develop two anti-fungal therapeutics in 2024. Similar to other ASPR/BARDA programs, the development supports pediatric patients and antifungal susceptibility testing (AST) diagnostics to ensure the protection of all age groups. ASPR/BARDA led the establishment of the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) program, a global public-private partnership dedicated to accelerating early-stage antibacterial innovation.[9,23] ASPR/BARDA continues to be the largest funder to CARB-X with NIH/NIAID providing preclinical services to approximately 50 percent of the CARB-X projects.[22] Through the CARB-X platform and through its advanced research and development programs, ASPR/BARDA routinely works with ten global partners to meet shared goals for new classes of antimicrobial products.[22]

The HHS Advanced Research Projects Agency for Health (ARPA-H) is working to accelerate the discovery of new antibiotics, develop new models of utilizing the body's microbiome to prevent severe infection, and speed the

treatment of infections through ultra-fast diagnostics for pathogen identification and antibiotic susceptibility. Generative artificial intelligence (AI) and deep learning will be leveraged to expand the number of antibiotic candidates for pharmaceutical suitability.[19] Additionally, novel platforms will be developed to formulate precision blends of probiotics and prebiotics designed to outcompete harmful pathogens, prevent infection, and restore healthy microbiota.[24] APRA-H is also funding an effort that aims to overcome treatment-resistant bacterial vaginosis and enable new therapies for vaginal health.[25] Finally, ARPA-H is creating ultra-high throughput experimental platforms will identify the root causes of antibiotic resistance and will scan previously-unculturable microbes for the production of novel antibiotics.

The Department of Defense (DoD) supports promising first-in-class candidates and potential re-purposed approved drugs for evaluation as possible future wound infection or sepsis therapies.[22] The Defense Advanced Research Projects Agency (DARPA) and the Walter Reed Army Institute of Research (WRAIR) Experimental Therapeutics Branch are using novel AI algorithms to discover novel small molecules with activity against multidrug-resistant bacteria.[22]

Clinical Research toward Regulatory Approval

Clinical trials required for regulatory approval are costly and challenging.
When conducting clinical trials for AM drugs to treat resistant infections, individual trial sites may see very few eligible patients, resulting in protracted timelines to accrue sufficient patients for the trial. In addition, these patients may have co-morbidities or receive concomitant AM drugs, making assessment of a treatment benefit for the investigational drug difficult.[26] These challenges may lead developers to pursue regulatory approval for more common indications rather than more complicated infections. Even if the drug candidate has potential to treat resistant infections, evidence of this may not appear in regulatory filings or published literature.

U.S. Government efforts
The Centers for Disease Control and Prevention (CDC) and FDA Antimicrobial Resistance Isolate Bank provides unique assets for drug developers, related drug and diagnostic industry counterparts, and laboratory directors and researchers to find the latest and highest-quality antimicrobial-resistant isolates available. These represent "isolates for action" that include a subset of known microbial threats collected from CDC's ongoing surveillance, outbreak activities, and external collaborators. The AR Isolate Bank then combines these samples into panels for testing that are aligned with expected new drug approvals and serve as challenge sets for preclinical development pipelines, and well as associated diagnostic platforms that are crucial for testing and therapy decisions that ensue.

NIH/NIAID supports the Antibacterial Resistance Leadership Group (ARLG), which has established collaborations with over 150 clinical trial sites across 19 countries and conducted over 65 clinical research studies involving more than 28,000 participants to address key questions in AMR research and improve patient care.[22,27]

ASPR/BARDA reduces barriers to antimicrobial drug development through the formation of public-private partnerships with industry. Working with other federal partners supporting early-stage development, ASPR/BARDA partnerships advance candidates from Phase 1 clinical development into late-stage clinical development, providing non-dilutive funding and subject matter expertise to accelerate the drug development process. This support spans numerous development areas, including Phase 1, 2, and 3 clinical trials; nonclinical studies; chemistry, manufacturing and controls; quality and regulatory; post-marketing commitments; and label expansion studies. Through Project BioShield authorities, ASPR/BARDA also has the ability to procure product for national preparedness.

FDA facilitates AM drug development by providing scientific and regulatory advice to drug sponsors at all stages of development. This work includes FDA guidance and workshops for industry that discuss scientific approaches to clinical trial design to foster and guide AM drug development.[22] The Generating Antibiotic Incentives Now (GAIN) Act of 2012 created the Qualified Infectious Disease Product (QIDP) designation, which provides incentives for the development of certain antimicrobial products, including access to several FDA expedited development and review programs.[28] As of March 2023, FDA had approved 33 QIDP products for bacterial or fungal infections, though the number of QIDP designations has declined in recent years (see Figure 3).[29] In addition, development may be streamlined for certain AM drugs designed to treat a serious or life-threatening infection in a limited population of patients with unmet needs, under the Limited Population Antibacterial Drug (LPAD) Pathway created by the 21st Century Cures Act of 2016.[30] As of February 2024, FDA had approved three products[†] under the LPAD pathway.[30]

Post-approval

Appropriate uptake and use of novel AM drugs is limited.

In addition to informing regulatory review, scientific evidence about new classes of AM drugs informs their uptake by clinicians and hospitals. When available, this evidence can be incorporated into clinical practice guidelines. However, the clinical trials challenges described above may limit the evidence available to support these decisions. In addition, appropriate use of AM drugs should be supported by diagnostic testing, including the use of ASTs, which can guide clinicians by clarifying which AM drugs are likely to be effective in treating a given patient. These tests need to be developed, used, and then updated as resistance patterns of bacteria and fungi change over time. Uptake of novel AM drugs may also be impacted by payment policies for hospitals for the treatment of infections. For example, the Medicare program makes bundled payment to hospitals for inpatient services and has an outlier payment policy for very costly cases.[31]

U.S. Government efforts to facilitate appropriate use of novel AM drugs

CDC's Antimicrobial Resistance Solutions Initiative supports innovative approaches to developing and deploying diagnostic tests and treatment strategies to address AMR and works with partners to discover, implement, and evaluate innovative strategies to improve healthcare quality, infection prevention, and patient safety. CDC develops guidance for appropriate use of AM drugs (*Core Elements of Antibiotic Stewardship*) and works with guidelines developers (e.g., the Infectious Diseases Society of America or IDSA) and standards bodies (e.g., the Clinical & Laboratory Standards Institute or CLSI) to inform and improve guidelines for the diagnosis and treatment of infectious diseases. While not directly supported by the U.S. Government, IDSA has begun updating relevant guidance documents more frequently to ensure that clinicians receive timely information about new treatments.[32] CDC also conducts research on AM drug utilization and prescribing trends and educates healthcare professionals and the general public about appropriate antibiotic use.

CDC also recently released a new resource to improve diagnostic testing in hospitals, *the Core Elements of Hospital Diagnostic Excellence*.[33] The Core Elements outline actionable practices for hospitals to improve diagnoses including diagnostic reasoning, testing, and communication activities, thereby improving patient safety. CDC developed the Core Elements in consultation with the Agency for Healthcare Research and Quality (ARHQ) and the Centers for Medicare & Medicaid Services (CMS). The framework was also informed by expert knowledge within the clinical and patient community.

[†] Arikayce on 9/28/2018 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/207356Orig1s000ltr.pdf
Pretomanid on 8/14/2019 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/212862Orig1s000ltr.pdf
Defencath on 11/15/2023 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/214520Orig1s000ltr.pdf

ASPR/BARDA supports the advanced development of diagnostic tests, specifically AST systems as an *in vitro* test to determine the susceptibility of isolated colonies of specific bacteria and AST systems for quantitative and qualitative testing of priority bacterial pathogens. Current actions supported by ASPR/BARDA toward responsible stewardship and equitable access to antibiotics include the collaborative development of the world's first Stewardship and Access Plan Development Guide, which CARB-X product developers are contractually obligated to develop as the product enters pivotal clinical trials (generally Phase 3 or equivalent for diagnostics). These plans support responsible stewardship and appropriate access in low- and middle-income countries (LMICs).

To support the development of novel diagnostics and thereby inform the appropriate use of AM drugs, CDC and the FDA AR Isolate Bank have shared more than 400,000 isolates from healthcare, food, and community settings to diagnostic test developers at no cost other than shipping.[22] Additionally, these isolates have been essential to the required regulatory needs for clinical laboratory directors to validate and verify diagnostic updates approved by FDA and generated by consensus standards bodies such as CLSI. NIH/NIAID supports development of novel diagnostic platforms that bypass overnight blood culture to rapidly identify pathogens and predict antimicrobial susceptibility or resistance to determine optimal treatment and clinical follow-up. In 2023, NIH/NIAID established a new program offering a comprehensive array of in-kind preclinical services to diagnostic developers to accelerate progress toward regulatory clearance and commercial launch.[22]

Since 2015, FDA has cleared or approved more than 200 diagnostics to help determine antimicrobial susceptibility and detect antimicrobial-resistant pathogens.[34,35] In a 2019 Guidance for Industry, FDA encouraged sponsors to coordinate parallel development of AM drugs and relevant AST devices, with the goal to streamline the review process and limit the time between new AM drug approvals and AST clearance.[36] Additionally, in September 2023, FDA's Center for Devices and Radiological Health (CDRH) issued a guidance "Antimicrobial Susceptibility Test (AST) System Devices –Updating Breakpoints in Device Labeling".[37] This guidance describes least burdensome approaches for AST system device manufacturers to update their device labeling with the updated breakpoints listed on the FDA's susceptibility test interpretive criteria (STIC) website. The policy and recommendations described in this guidance are expected to facilitate the timely adoption of updated breakpoints in AST system devices, which helps to ensure device safety and effectiveness.

Traditional Medicare (fee-for-service) has enacted changes in the ways hospitals are paid to facilitate access to newly-approved AM drugs.[38] Certain newly-approved AM drugs with QIDP designation or approved under the LPAD approval pathway qualify for increased New Technology Add-on Payments (NTAP) from Traditional Medicare, which provide added payment to hospitals for the period of the product's NTAP approval (typically two to three years).[39] These products are also deemed to meet Medicare's substantial clinical improvement criterion based on their QIDP designation or LPAD approval. Traditional Medicare designates discharges for patients with resistant infections as 'CC' (complications or comorbidities) for certain AMR-related ICD-10 codes, which often increases net payment to hospitals treating these patients. Hospitals may also receive an outlier payment from Traditional Medicare for very costly cases. Since Fiscal Year 2019, NTAP has provided an additional payment to hospitals of more than USD $24 million for eligible AM drugs, all of which had been QIDP-designated products (see Figure 3 and Table 1).[‡]

[‡] Inpatient, non-clinical trial NTAP payments, Fiscal Years 2019 through 2024

Figure 3. Number of antimicrobial products eligible for New Technology Add-on Payments (NTAP), Fiscal Years 2019 through 2024

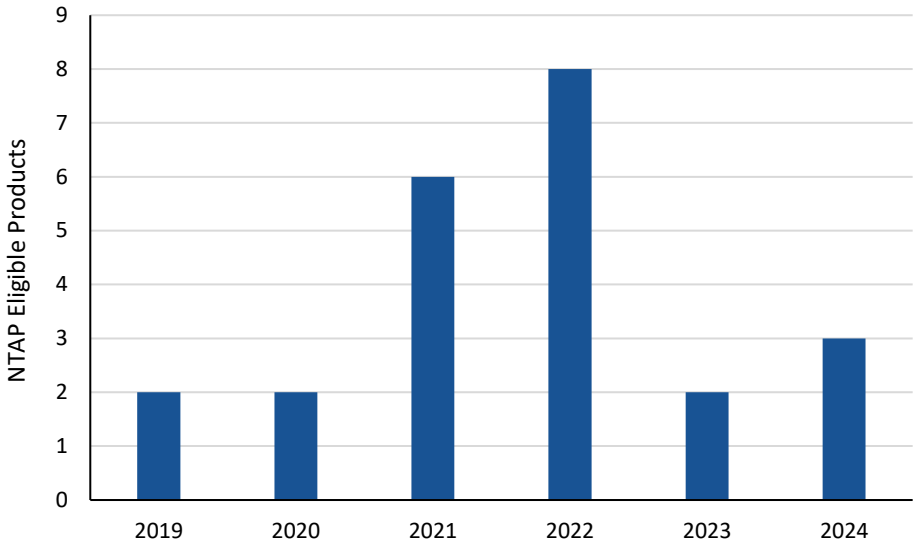


Table 1. Antimicrobial products eligible for New Technology Add-on Payments (NTAP), including total number of claims and amount of payments, Fiscal Years 2019 through 2024

Antimicrobial Technology	Generic Name	Indication(s)	Fiscal Years of NTAP eligibility	Total number of NTAP claims	Total amount of NTAP payments
Fetroja	Cefiderocol	cUTI/cIAI	2021-2022	1109	$9,000,894
Fetroja	Cefiderocol	HABP/VABP	2022-2023	30	$269,436
Nuzyra	Omadacycline	CABP/ABSSSI	2021-2022	91	$214,677
Recarbrio	Imipenem, cilastatin, and relebactam	cUTI/cIAI	2021-2022	336	$1,488,555
Recarbrio	Imipenem, cilastatin, and relebactam	HABP/VABP	2022-2023	3	$47,222
Rezzayo	Rezafungin for Injection	Candidemia and invasive candidiasis	2024	10	$38,899
Vabomere	Meropenem-vaborbactam	cUTI	2019-2020	930	$5,988,045
Xacduro	Sulbactam/Durlobactam	HABP/VABP due to *Acinetobacter baumanii-calcoaceticus* complex	2024	1	$13,680
Xenleta	Lefamulin	CABP	2021-2022	14	$49,626
Zemdri	Plazomicin	cUTI	2019-2022	16	$94,676
Zerbaxa	Ceftolozane and tazobactam	cUTI	2021-2022	2832	$8,309,952

Novel AM drugs generate low sales and therefore low revenue for sponsors.

After a novel AM drug is approved, sponsors may face continued costs that are not offset by sufficient sales revenue. Most AM drug development is currently undertaken by small- and medium-sized enterprises, which may be primarily focused on research and development. These companies may not have the necessary manufacturing and marketing capacity to adequately make and sell their products to generate revenue, and standing up these capacities is costly. These companies may also be required by FDA to fulfill post-marketing

commitments, including pediatric clinical trials, additional safety studies, and surveillance activity, all of which add to post-approval costs. To offset these costs, AM drug developers may be largely unable to simply charge more for their products, because hospitals are incentivized to use the lowest cost, clinically acceptable drug under Medicare's reimbursement system.

Even if these costs and pricing limitations were addressed, newly approved AM products should be used appropriately to minimize the risk of pathogens developing resistance. If sponsors are incentivized to sell more units of the drug than are necessary for appropriate patient care, that potential over-use could unnecessarily drive the development of pathogens resistant to those products, undermining their utility. However, the current payment structure links revenue with sales volume, and such low sales volume may be insufficient on its own to financially sustain AM drug sponsors.

U.S. Government efforts to increase and stabilize AM drug revenues

The U.S. Government has taken several actions to increase and stabilize revenues for AM drug sponsors. QIDP designation provides sponsors with an additional five years of marketing exclusivity, which protects branded-product sponsors from competition from generic versions of their products. Separately, the Project BioShield Act of 2004 was enacted to accelerate the research, development, purchase, and availability of effective medical countermeasures against biological, chemical, radiological, and nuclear (CBRN) threats.[40,41] To date, ASPR/BARDA has awarded two Project BioShield contracts for late-stage development and potential procurement of antibiotics to treat bacterial biothreats and drug-resistant bacterial infections. This effort supports label expansion, as well as late-stage post-approval clinical and manufacturing efforts that improve access to these products. ASPR/BARDA has leveraged $315M of Project BioShield funding to ensure these products are accessible to treat secondary drug-resistant bacterial infections following public health emergencies. As a secondary impact, Project BioShield provides funding while developers launch their products. Under Project BioShield, limited funding is available, so products are selected through a fair and open competitive review process for which any developer with an antimicrobial that meets posted requirements can apply.

Despite these supports, the AM drug pipeline continues to be meager and sponsors of newly-approved AM drugs have gone bankrupt. HHS has therefore concluded that additional significant incentives remain necessary. Two recent proposals, the PASTEUR Act[42] and a proposal in the President's Budget for Fiscal Year 2025[43], include a subscription-style incentive: the U.S. Government would provide annual payments to sponsors of innovative AM drugs regardless of the volume of drugs sold or used. The proposals aim to support developers of newly-approved AM drugs in the cost-intensive post-approval phase, to pay for ongoing clinical research, sales and marketing, and production costs. These proposals would complement existing incentives, creating a more comprehensive framework to support AM development from early-stage research to market access.[44]

Global registration of and access to novel AM drugs is limited.

Recent analyses of launch patterns among novel AM drugs indicate that they are typically launched in high-income countries (most frequently the United States) and that great variability exists across products as to whether and where products become registered and sold outside of the initial launch location. Notably, most newly FDA-approved AM drugs are sold in few if any lower income countries,[45] and many are not available even in high-income countries.[46] These analyses note the distinction between marketing authorization by a country's regulatory authority and commercial launch of sales and use in patient care; companies must invest in sales and marketing to support commercial launch, delaying further potential revenue from those sales.

A recent global analysis found that the burden of AMR, in terms of associated and attributable deaths at all ages, is highest in low- and middle-income countries, particularly sub-Saharan Africa and south Asia. These results indicate a mismatch between the global distribution of novel AM drug access and AMR burden. As

noted above, the domestic U.S. market for novel AM drugs is limited by the relatively small number of difficult-to-treat infections. If appropriately guided by diagnostics, antimicrobial stewardship principles, and regulatory oversight ensuring the availability of safe, effective, high-quality drugs, efforts to increase global access to novel AM drugs could both address dire public health needs and increase revenues for AM drug sponsors.

U.S. Government efforts to facilitate global access to novel AM drugs

Detecting and estimating the burden of AMR in global markets are components of supporting registration of and access to all AM drugs. CDC's Global Antimicrobial Resistance (AR) Laboratory and Response Network (Global AR Lab and Response Network) builds partner country capacity to improve the detection of existing and emerging AMR threats, by working in healthcare settings in low- and middle-income countries through programs like the Global Action in Healthcare Network (GAIHN) and the Antibiotic Resistance in Communities and Hospitals (ARCH) programs. These programs enable rapid action to slow the spread of novel AMR to existing and newly-approved AM drugs.

To harmonize regulatory approaches and enable AM drug sponsors to use the same or similar scientific evidence to support review and registration in multiple countries, FDA participates in multi-stakeholder national and international meetings with other regulatory agencies (e.g., European Medicines Agency, Health Canada, and Japan's Pharmaceuticals and Medical Devices Agency). Product developers that have received FDA approval with BARDA funding and technical expertise have been able to use the same data to support international regulatory filings and approvals in over 30 countries worldwide.

The United States Agency for International Development (USAID) AMR Access and Stewardship Initiative (AMRASI) is a new coalition of public- and private-sector stakeholders striving to design a proof-of-concept pilot that improves access to diagnostics and antimicrobials using market shaping interventions, while enabling appropriate use through stewardship and novel incentives.[47] For the pilot, AMRASI will work with one to three low- and middle-income countries (LMICs) to secure access to a portfolio of diagnostics and antibiotics that facilitate stewardship for respiratory tract infections. In addition to the pilot, the AMRASI coalition will establish a community of practice across more than 35 diverse organizations represented in the coalition to exchange insights, identify opportunities for collaboration, and accelerate implementation of approaches that combine access & stewardship to combat AMR in LMIC. The program's long-term aim is to improve the market dynamics that enable access to and appropriate use of antimicrobials in LMICs, thus facilitating novel AM drug uptake and use in areas of high AMR burden.

Future Opportunities

While several of the efforts described above have been implemented in recent years, stakeholders continue to point to the insufficient pipeline of AM drugs in development and to the financial challenges facing sponsors of newly-approved AM drugs. To address these challenges, the U.S. Government and its global public and private partners could consider additional opportunities to amplify the impact of existing efforts and expand the scope of strategies to ensure the availability of effective AM treatments into the future. CDC maintains a bacterial priority pathogens list that serves as an important resource to guide U.S. policy for investments in combating AMR.[5] However, policy efforts to improve the pipeline for AM drugs would greatly benefit from additional clarity and structure around how to define a sustainable and successful AM drug development and access ecosystem. Policymakers should work toward an AM drug ecosystem that ensures that infectious diseases can be treated effectively into the future despite the evolution of AMR.

U.S. Government investments to date have played a major role in revitalizing the antimicrobial pipeline and promoting global interest in the private sector to address antimicrobial resistance. Strategic public-private partnerships have a proven track record in navigating the inherent challenges associated with increasing expense and the lack of a clear return on investment for AM drug development. In addition to the sustained

funding levels supporting AM drug development, an immediate action to bolster private investments will require increased funding to address the rising rate of antimicrobial resistance.

The subscription-model proposals described above would require enactment and funding by the U.S. Congress to implement, and if enacted, details of the program would need to be specified to ensure maximum effectiveness. To ensure the best value for U.S. Government implementation, the proposals would require adequate flexibility to accelerate program set up and to quickly respond to future changes in AMR and in the AM drug market. A considerable challenge to implementing these proposals is defining how to appropriately value the designated products. Relevant novel AM drugs should address critical unmet needs, which would encompass products that address emerging pathogens, those resistant to current AM products, or those that cause infections for which limited treatments are currently available. Novel mechanisms of action and appropriate formulations could also be used to determine the value of a contract. Importantly, the goal of these proposals is to address failures of the open market to appropriately reward the broader public health value of novel AM drugs, so a product's valuation under the program must exceed its "market" valuation.

The global burden of resistant infections is high, but novel products are often not accessible outside of the U.S., even in other high-income countries.[46] Even with optimal clinical uptake, the U.S. market alone is likely too small to sustain sponsors of newly-approved AM drugs. Policies and programs could be developed or expanded with the aim to improve access to newly FDA-approved AM drugs in across geographies that currently lack access, including areas of highest AMR burden, particularly low- and middle-income countries (LMICs). Such efforts need to account for the considerable costs and effort required for regulatory approval, quality assurance, and antibiotic stewardship in low-resource healthcare settings.

An important strategy to help mitigate the global burden of AMR is to interrupt the transmission of and infections caused by resistant pathogens in healthcare settings through infection prevention and control measures. In addition to development of novel AM drugs and the diagnostics necessary for their appropriate use, there is also a need for novel products that reduce pathogen burden (such as decolonization agents), thus decreasing infections and transmission. In addition to direct benefit to the decolonized patient, modeling studies have found that the indirect benefits beyond the patient treated make pathogen reduction products cost-effective.[48] CDC, FDA, NIH, BARDA, and other federal partners have initiated pilot efforts to address R&D and regulatory challenges in order to bring these novel products to fruition, but additional investment is needed to realize their full impact.[49,50]

Conclusions

The United Nations General Assembly held a High-Level Meeting on AMR on September 26, 2024, where global leaders approved a Political Declaration that includes a target of a 10 percent reduction in deaths associated with bacterial antimicrobial resistance by 2030. To accomplish this, Member States committed to working toward increasing global access to and appropriate use of antimicrobials in areas of high AMR burden, and to exploring innovative incentives for research and development to address AMR. The U.S. Government efforts described here support those commitments, and the additional policy opportunities would further strengthen the U.S. Government's comprehensive approach to sustainable AM drug availability, particularly during the critical post-approval phase. As we work to develop the third iteration of the National Action Plan for CARB, the U.S. Government remains committed to combating AMR through coordinated and strategic action under a One Health approach and will continue efforts to accelerate research and development toward a future where AM drugs are sustainably available.

REFERENCES

1. Centers for Disease Control and Prevention (U.S.) National Center for Emerging and Zoonotic Infectious Diseases (U.S.) Division of Healthcare Quality Promotion. *Antibiotic Resistance Threats in the United States, 2019*. 2019. https://stacks.cdc.gov/view/cdc/82532
2. Antimicrobial Resistance Collaborators. Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis. *Lancet*. Feb 12 2022;399(10325):629-655. doi:10.1016/S0140-6736(21)02724-0
3. GDB 2021 Antimicrobial Resistance Collaborators. Global Burden of Bacterial Antimicrobial Resistance 1990-2021: A Systematic Analysis with Forecasts to 2050. *Lancet*. Sep 28 2024;404(10459):1199-1226. doi:10.1016/S0140-6736(24)01867-1
4. Centers for Disease Control and Prevention (U.S.) National Center for Emerging and Zoonotic Infectious Diseases (U.S.) Division of Healthcare Quality Promotion. Division of Healthcare Quality Promotion. *COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022*. 2022. https://stacks.cdc.gov/view/cdc/119025
5. Centers for Disease Control and Prevention (U.S.). *Antimicrobial Resistance Threats in the United States, 2021-2022*. 2024. https://www.cdc.gov/antimicrobial-resistance/data-research/threats/update-2022.html
6. McDonnell A CA, Laurence T, Gulliver S, Drake T, Edwards S, Kenny C, Lamberti O, Morton A, Shafira A, Smith R, Guzman J. Forecasting the Fallout from AMR: Economic Impacts of Antimicrobial Resistance in Humans – A report from the EcoAMR series. *Paris (France) and Washington, DC (United States of America): World Organisation for Animal Health and World Bank*. 2024:58. doi:10.20506/ecoAMR.3539
7. Nelson RE, Hatfield KM, Wolford H, et al. National Estimates of Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Hospitalized Patients in the United States. *Clin Infect Dis*. Jan 29 2021;72(Suppl 1):S17-S26. doi:10.1093/cid/ciaa1581
8. World Health Organization (Geneva). WHO fungal priority pathogens list to guide research, development and public health action. https://www.who.int/publications/i/item/9789240060241
9. Piddock LJV, Alimi Y, Anderson J, et al. Advancing Global Antibiotic Research, Development and Access. *Nat Med*. Sep 2024;30(9):2432-2443. doi:10.1038/s41591-024-03218-w
10. Federal Task Force for Combating Antibiotic-Resistant Bacteria. *National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025*. 2020. https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant-bacteria-2020-2025
11. World Health Organization (Geneva). Library of AMR National Action Plans. https://www.who.int/teams/surveillance-prevention-control-AMR/national-action-plan-monitoring-evaluation/library-of-national-action-plans
12. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. https://www.hhs.gov/ash/advisory-committees/paccarb/index.html
13. Federal Task Force for Combating Antibiotic-Resistant Bacteria. https://aspe.hhs.gov/collaborations-committees-advisory-groups/carb
14. World Health Organization (Geneva). 2023 Antibacterial Agents in Clinical and Preclinical Development: An Overview and Analysis. https://www.who.int/publications/i/item/9789240094000
15. Jesudason T. Antibacterial Agents in Preclinical and Clinical Development. *The Lancet Microbe*. 2024;5(10)doi:10.1016/j.lanmic.2024.100962
16. Sertkaya A, Berlind A, McGeeney JD, Berger C, Stokes-Cawley O. *Analysis of Market Challenges for Antimicrobial Drug Development in the United States: Final Report*. 2022. *HHS ASPE Reports*. https://www.ncbi.nlm.nih.gov/pubmed/38691034
17. Sullivan C, Kolbe A. *Understanding Markets for Antimicrobial Drugs: Issue Brief*. 2023. *HHS ASPE Reports*. https://www.ncbi.nlm.nih.gov/pubmed/38691037
18. Melchiorri D, Rocke T, Alm RA, Cameron AM, Gigante V. Addressing Urgent Priorities in Antibiotic Development: Insights from WHO 2023 Antibacterial Clinical Pipeline Analyses. *Lancet Microbe*. Oct 22 2024:100992. doi:10.1016/j.lanmic.2024.100992
19. Advanced Research Projects Agency for Health. ARPA-H Project to Accelerate the Discovery of New Antibiotics using AI. https://arpa-h.gov/news-and-events/arpa-h-project-accelerate-discovery-and-development-new-antibiotics-using
20. Sertkaya A, Franz C, Berger C, Stokes-Cawley O. *Antimicrobial Drugs - Market Returns Analysis*. 2023. *HHS ASPE Reports*. https://aspe.hhs.gov/reports/antimicrobial-market-returns
21. U.S. National Institutes of Health National Institute of Allergy and Infectious Diseases. Chemistry Center for Combating Antibiotic Resistant Bacteria (CC4CARB). https://www.cc4carb-collection.org/

22. Federal Task Force for Combating Antibiotic-Resistant Bacteria. *National Action Plan for Combating Antibiotic-Resistant Bacteria Progress Report: Fiscal Year 2022*. 2024. https://aspe.hhs.gov/reports/carb-fy22-report
23. Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator. https://carb-x.org/
24. Advanced Research Projects Agency for Health. HHS announces ARPA-H project to prevent infections and limit reliance on antibiotics. https://arpa-h.gov/news-and-events/hhs-announces-arpa-h-project-prevent-infections-and-limit-reliance-antibiotics
25. Advanced Research Projects Agency for Health. Sprint for Women's Health. https://arpa-h.gov/engage-and-transition/sprint
26. Ghosh M, Iarikov D, Qi XK, et al. Flexible Development Programs for Antibacterial Drugs to Address Unmet Medical Needs. *Emerg Infect Dis*. Nov 2024;30(11):2227-2230. doi:10.3201/eid3011.231416
27. Antibacterial Resistance Leadership Group. https://arlg.org/
28. U.S. Food and Drug Administration. Qualified Infectious Disease Product Designation-Questions and Answers; Guidance for Industry. Federal Information & News Dispatch, LLC. 86. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualified-infectious-disease-product-designation-questions-and-answers
29. U.S. Food and Drug Administration. Data from: Pink Sheet - QIDP Designations. 2022.
30. U.S. Food and Drug Administration. Limited Population Pathway for Antibacterial and Antifungal Drugs – the LPAD Pathway. https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway
31. Strich JR, Mishuk A, Diao G, 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*. May 2024;177(5):559-572. doi:10.7326/M23-2309
32. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections. *Clin Infect Dis*. Aug 7 2024;doi:10.1093/cid/ciae403
33. Centers for Disease Control and Prevention. Core Elements of Hospital Diagnostic Excellence (DxEx). https://www.cdc.gov/patient-safety/hcp/hospital-dx-excellence/index.html
34. U.S. Food and Drug Administration. Antimicrobial Resistance. https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/antimicrobial-resistance
35. Federal Task Force for Combating Antibiotic-Resistant Bacteria. *National Action Plan for Combating Antibiotic-Resistant Bacteria Progress Report: Year 5*. 2022. https://aspe.hhs.gov/reports/carb-year-5-report
36. U.S. Food and Drug Administration. Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/coordinated-development-antimicrobial-drugs-and-antimicrobial-susceptibility-test-devices
37. U.S. Food and Drug Administration. Antimicrobial Susceptibility Test (AST) System Devices – Updating Breakpoints in Device Labeling. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/antimicrobial-susceptibility-test-ast-system-devices-updating-breakpoints-device-labeling
38. Centers for Medicare & Medicaid Services. Fact Sheet: Fiscal year (FY) 2020 Medicare Hospital Inpatient Prospective Payment System (IPPS) and Long Term Acute Care Hospital (LTCH) Prospective Payment System (CMS-1716-F). https://www.cms.gov/newsroom/fact-sheets/fiscal-year-fy-2020-medicare-hospital-inpatient-prospective-payment-system-ipps-and-long-term-acute-0
39. Centers for Medicare & Medicaid Services. New Medical Services and New Technologies. https://www.cms.gov/medicare/payment/prospective-payment-systems/acute-inpatient-pps/new-medical-services-and-new-technologies
40. S.15 - 108th Congress (2003-2004). Project BioShield Act of 2004. https://www.congress.gov/bill/108th-congress/senate-bill/15
41. Administration for Strategic Preparedness and Response. Project Bioshield. https://medicalcountermeasures.gov/barda/cbrn/project-bioshield/
42. S.1355 - 118th Congress (2023-2024). PASTEUR Act of 2023. 2023;
43. U.S. Office of Management and Budget. Budget of the United States Government - Fiscal Year 2025. https://www.whitehouse.gov/wp-content/uploads/2024/03/budget_fy2025.pdf
44. Organizations Focused on Fight Against Superbugs Celebrate Reintroduction of the PASTEUR Act. 2023. https://www.pewtrusts.org/en/about/news-room/press-releases-and-statements/2023/04/27/organizations-focused-on-fight-against-superbugs-celebrate-reintroduction-of-the-pasteur-act
45. Kallberg C, Ardal C, Salvesen Blix H, et al. Introduction and Geographic Availability of New Antibiotics Approved Between 1999 and 2014. *PLoS One*. 2018;13(10):e0205166. doi:10.1371/journal.pone.0205166

46. Outterson K, Orubu ESF, Rex J, Ardal C, Zaman MH. 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*. Apr 9 2022;74(7):1183-1190. doi:10.1093/cid/ciab612
47. U.S. Agency for International Development Center for Innovation and Impact. INCUBATE: USAID Launches New Project to Combat Antimicrobial Resistance. *Innovation + Impact E-Newsletter*.
48. Toth DJA, Samore MH, Nelson RE. Economic Evaluations of New Antibiotics: The High Potential Value of Reducing Healthcare Transmission Through Decolonization. *Clin Infect Dis*. Jan 29 2021;72(Suppl 1):S34-S41. doi:10.1093/cid/ciaa1590
49. Mangalea MR, Halpin AL, Haile M, Elkins CA, McDonald LC. Decolonization and Pathogen Reduction Approaches to Prevent Antimicrobial Resistance and Healthcare-Associated Infections. *Emerg Infect Dis*. Jun 2024;30(6):1069-1076. doi:10.3201/eid3006.231338
50. U.S. Centers for Disease Control and Prevention. Drug Development Considerations for the Prevention of HAIs https://www.youtube.com/watch?v=Ki39lSM3_ok

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Assistant Secretary for Planning and Evaluation

200 Independence Avenue SW, Mailstop 434E
Washington, D.C. 20201

For more ASPE briefs and other publications, visit:
aspe.hhs.gov/reports

ABOUT THE AUTHORS
Casey Sullivan is a Social Science Analyst in the Office of Science and Data Policy in the Office of the Assistant Secretary for Planning and Evaluation. *Cody R. Fisher* is a Social Science Analyst in the Office of Science and Data Policy in the Office of the Assistant Secretary for Planning and Evaluation. *Julia Taenzer* is an ORISE fellow in the Office of Science and Data Policy in the Office of the Assistant Secretary for Planning and Evaluation.

SUGGESTED CITATION
Sullivan, C., Fisher, C. R., & Taenzer, J. Novel Antimicrobial Drug Development and Access: U.S. Government Support and Opportunities. Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services. November 2024.

ACKNOWLEDGMENTS
The authors thank Kim Nguyen (ASPE), Michael Lanthier (FDA), Jessica Swenson (BARDA), Catherine Bernstein (CMS), and the U.S. Task Force for Combating Antibiotic-Resistant Bacteria.

For general questions or general information about ASPE:
aspe.hhs.gov/about