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

ISSUE BRIEF
AUGUST 2023

Understanding Markets for Antimicrobial Drugs

KEY POINTS

- Development of novel antimicrobials has slowed, and the preclinical and clinical pipeline is likely to be insufficient to support current and future patient needs.
- Despite existing incentives, market challenges limit the revenues that novel antimicrobial drug sponsors can receive, leading smaller developers to struggle financially and larger companies to divest from antimicrobial research and development.
- Ongoing and future patient access to antimicrobial products can be supported alongside antibiotic stewardship goals through significant additional financial incentives that provide a predictable revenue stream for sponsors, particularly those that are "de-linked" from the volume of product sales.

OVERVIEW

Antimicrobial (AM) drugs revolutionized the treatment of infectious diseases in the 20th century. However, bacteria and fungi continuously evolve resistance and new pathogens emerge, making AM drugs less effective over time, eroding clinicians' ability to treat patients, and driving the need to discover new AM drugs. Each year, the U.S. Centers for Disease Control and Prevention (CDC) estimate that more than 2.8 million antibiotic-resistant infections occur in the United States and more than 35,000 people die as a result, and resistance to many commonly used AM drugs continues to rise in the U.S. and abroad.[1,2] Recent progress toward reducing the impact of antimicrobial resistance was largely reversed during the first year of the COVID-19 pandemic, as antibiotic use (much of it clinically inappropriate) and resistant infections increased.[3]

In addition to addressing the current burden of resistant infections, the continual evolution of resistance means that a continual pipeline of new products is needed to ensure that effective treatments are available in the future. However, development of novel and innovative AM drugs has slowed in recent decades, despite the potential for new AM drugs to reduce the social burden associated with resistant infections.[4] The World Health Organization has analyzed the preclinical and clinical pipeline annually since 2017, and in each analysis has concluded that the limited number of antibiotics in development is insufficient to address current and future patient needs.[5]

For many years, HHS has been working to understand the factors that cause an insufficient AM drug pipeline. These efforts have involved analyzing existing federal initiatives and external proposals and seeking the perspectives of stakeholders from investment, industry, advocacy, and healthcare. The overarching goal of this work is to inform the development and implementation of policies that ensure access to effective AM drugs now and into the future. These efforts support Goal 4 of the U.S.

National Strategy for Combating Antibiotic-Resistant Bacteria,[6] which aims to accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.

As part of this effort, ASPE partnered with the Food and Drug Administration (FDA) to fund an economic analysis of the AM drug market. Conducted by Eastern Research Group, Inc. (ERG) in collaboration with a Project Advisory Group of HHS staff,[i] the project assessed development costs and subsequent revenues for AM drugs, examined estimates of the future economic and health burden of antimicrobial resistance, and evaluated market failures for AM drugs. Three reports published alongside this issue brief provide the results of this analysis: *Antimicrobial Drugs – Burden of Antimicrobial Resistance, Analysis of Market Challenges for Antimicrobial Drug Development in the United States, and Antimicrobial Drugs Market Returns Analysis*. Overall, ERG found that the current market for AM drugs includes a range of challenges that result in sponsor revenues that are insufficient to develop and commercialize novel AM drugs at a level to meet public health and national security needs.

This issue brief was developed by ASPE to accompany ERG's reports. Here we synthesize ERG's results with HHS's analyses and discuss policy options to address the challenges to the AM drug market.

ESTIMATING THE BURDEN OF ANTIMICROBIAL RESISTANCE

The current market for hypothetical novel AM drugs can be thought of as the unmet need: the number of patients for whom these products would be used appropriately. Given that any antibiotic use puts evolutionary pressure on pathogens and can provide opportunity for resistance to develop, novel AM drugs are typically not recommended for widespread and empiric use. That is, keeping novel AM drugs "in reserve" maintains their effectiveness for when they are truly needed. The current market for novel AM drugs therefore includes patients whose infections are resistant to existing first-line or subsequent treatments, or others for whom additional treatment options are needed. While a troubling share of infections are resistant to specific drugs or classes of drugs,[ii] truly difficult-to-treat infections that are resistant to all safe and effective first-line treatments are still relatively rare in the U.S. For example, a recent study estimated that only about 1% of treatment opportunities for Gram-negative infections were resistant to all first-line antibiotics and therefore had few or no routine treatment options.[7] Thus, the patient population for novel AM drugs is relatively small, though these patients tend to have worse outcomes than those whose with at least one safe and effective treatment option.[8] Even when novel AM drugs are used, the course of treatment is typically short compared to products that treat chronic diseases. Therefore, the current U.S. market for novel AM drugs can be considered relatively small compared to other new small-

[i] The Project Advisory Group included representatives from FDA, CDC, the National Institutes of Health (NIH), and the Administration for Strategic Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA). The research conducted by ERG was funded by ASPE under Contract Number HHSP233201500055I, Task Number HHSP23337006T, with funds provided to ASPE by the FDA under Interagency Agreements 224-18-3013S and 75F40119S30008.

[ii] The proportion of infections that are resistant to specific drugs varies by pathogen and by drug. However, for example, CDC found that 29.3% of *Streptococcus pneumoniae* isolates tested by the Active Bacterial Core Surveillance Program in 2020 were resistant to erythromycin. Centers for Disease Control and Prevention. 2020. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, *Streptococcus pneumoniae*, 2020. Available at: https://www.cdc.gov/abcs/downloads/SPN_Surveillance_Report_2020.pdf

molecule drug products, putting a functional cap on the sales and revenues these products could generate on the open market.

The size of the future market for novel AM drugs depends on how resistance to current AM drugs changes over time. Implementation of improved infection prevention and control, and high-quality antibiotic stewardship programs, can slow the spread of antibiotic resistance, and helped reduce the rates of resistant infections and resulting deaths in the years immediately prior to the COVID-19 pandemic. Such efforts will continue to be vital to maintaining the effectiveness of current AM drugs into the future.

However, all AM drug use, however appropriate, exerts evolutionary pressure that selects for microbial strains that survive treatment. As resistance to current AM drugs develops, new products will be needed to replace them. Understanding the scope of that future need, in terms of the projected number of infections, of which types, and how these needs may emerge over time, would be extremely informative for policy development. These kinds of projections would enable policy makers to target actions toward addressing specific anticipated outcomes (e.g., a need for AM drugs effective against specific pathogens) and to appropriately scale a policy action (e.g., a need to support one or two new AM drugs vs. more). ASPE worked with ERG to understand the feasibility of developing projections of the future health and economic burden of AMR.

ERG's report concluded that the future burden of AMR is very difficult to estimate. ERG's *Antimicrobial Drugs – Burden of Antimicrobial Resistance* report provides a systematic review of existing literature estimates of 15 pathogen-drug combinations and describes the challenges to estimating the health and economic burden of AMR. The report draws data from published studies on mortality, length of stay, and healthcare costs for resistant and susceptible infections from various infection sites. ERG concluded that none of the 15 pathogen-drug combinations had sufficient existing literature to support infection-site-specific AMR burden modeling, and studies that aggregate across infection sites were scarce and raised questions about generalizability. Other authors have also recently concluded that the state of AMR forecasting is "still not mature enough" to inform targeted public health or policy decisions.[9]

However, the unpredictable evolutionary trajectory of AMR itself presents a risk that necessitates the development of novel AM drugs. New forms of resistance emerge, as with the recent discovery and spread of *Candida auris*, which is now listed among CDC's urgent threats.[10] Barring an unforeseen scientific innovation that changes the trajectory of microbial evolution, novel AM drugs will be continuously needed to treat infections as resistance to current AM drugs evolves. Given that projections of future AMR burden would inform and improve more targeted policy development, HHS continues work to understand the data and methodological challenges to these projections and how to address them.

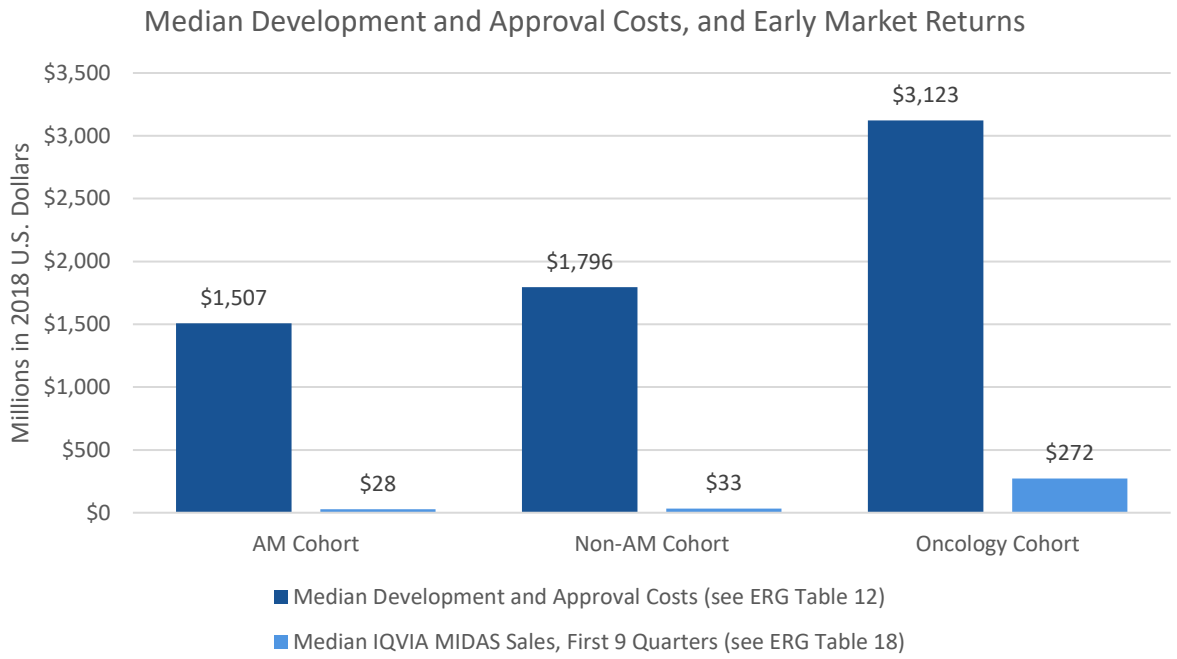
MARKET RETURNS FOR NOVEL ANTIMICROBIAL DRUGS

Examining the state of novel AM drug development can help to understand the impact of existing incentives and identify whether further incentives are necessary. In their *Analysis of Market Challenges for Antimicrobial Drug Development in the United States*, ERG examined patents as an indicator of the robustness of early-stage development, and found that the average number of

patents per year for antibacterial compounds has actually been increasing in the last ten years at a rate similar to patents for other pharmaceutical compounds. However, a subsequent analysis indicated that commercial companies' share of antibacterial patents declined by 32% between 1990 and 2021, with universities, non-governmental organizations, and governments making up an increasing share of the patent filers for antibacterial compounds.[11] This result echoes the shift in clinical development activities over time from large companies to small or mid-sized companies.[12]

Despite this indication of early-stage innovation, the number of new antibacterial drug approvals in the U.S. has generally declined over time since at least the 1980s,[12] with no novel antibacterial approvals between 2020 and Q1 2023. ERG's *Antimicrobial Drugs Market Returns Analysis* examined development and production costs and early market performance of a cohort of recently approved AM drugs, compared with two cohorts of other product types. The choice of comparison cohorts was complicated by the unique features of the novel AM drugs, including being hospital administered, with short treatment durations, and being reimbursed by Medicare as part of diagnosis-related group (DRG) "bundles". Hospitals are usually reimbursed the same amount for a bundle regardless of whether the patient receives a more expensive novel branded AM drug or a less expensive older generic AM drug. Stakeholders have argued that this reimbursement structure drives hospitals away from using novel AM drugs, because they are not fully reimbursed for those higher costs.[13] Through consultation with the Project Advisory Group, ERG developed one comparison cohort of non-antimicrobial products that are also administered in hospitals, with short treatment durations, and reimbursed under Medicare diagnosis-related groups (DRGs). The Project Advisory Group chose oncology products as the other comparison cohort to understand the potential return-on-investment that a product sponsor might choose in pursuit of relatively higher profits. Medicare reimbursement for oncology products does not typically fall within the DRG-based bundles, but rather is calculated individually for each product. This reimbursement structure avoids hospitals' incentive to manage costs within the DRG bundles, and potentially allows product sponsors more leverage in pricing these products. To evaluate whether market performance might be related to clinical utility, the authors also developed a novel method of assessing comparative added clinical benefit using publicly available metrics.

ERG's results indicate that AM drugs have relatively low development and approval costs compared to oncology drugs (and similar to comparable non-AM drugs). However, AM drugs also have lower early market sales than comparable non-AM drugs, and much lower early market sales than oncology drugs. These results suggest that sponsors may avoid AM product development because they are relatively less profitable than other pharmaceutical classes.



Interestingly, ERG's analysis suggests that products with relatively higher comparative added clinical benefit tend to show relatively higher early market sales compared to other products within the same cohort. This result suggests that beneficial products can differentiate themselves and potentially see improved revenues. However, interpretation of that result should be limited given the current study's focus on recently approved AM drugs, which resulted in a small sample size and limited data available for this analysis. Additional research could explore whether this comparative added clinical benefit assessment is robust across other therapeutic areas or longer time periods.

MARKET CHALLENGES FOR NOVEL ANTIMICROBIAL DRUG DEVELOPMENT

As discussed above, the current market for novel AM drugs is relatively small compared to the market for products that treat more widespread or chronic conditions. It is also compounded by several specific market challenges, which had been identified by HHS and elsewhere[14] but which were confirmed by the expert interviews conducted by ERG for their *Analysis of Market Challenges for Antimicrobial Drug Development in the United States*. In this report, ERG points out that market failure is the norm for biopharmaceutical markets in general, because these markets are not perfectly competitive from an economic standpoint. However, several challenges specific to the AM drug market add to and potentially exacerbate the effects of market-wide challenges, including:

Clinical trial challenges: Sponsors of AM drugs to treat resistant infections face many challenges in efficiently evaluating their safety and efficacy. Any single clinical trial site may see very few patients with resistant infections, and these patients often have multiple co-morbidities making assessment of treatment benefit difficult. The safety and efficacy of new AM drugs for the treatment of serious infections are most frequently evaluated using non-inferiority trials, which show that the new drug is no worse than the active comparator standard treatment by a pre-specified margin. In contrast, superiority trials (or comparative effectiveness studies) can

demonstrate whether a new drug works significantly better than the standard treatment. Furthermore, developers often choose to conduct trials for common indications, such as complicated urinary tract infections, rather than more complicated infections that might otherwise differentiate the novel drug from existing AM drugs. Together, these factors may result in a lack of compelling clinical trial evidence to support payers, hospitals, and clinicians' choices of some novel AM drugs over more familiar, less expensive generic AM drugs.[15]

Clinical practice challenges: Clinical practice guidelines are critical to informing appropriate health care practice and treatments for specific circumstances, and can influence the inclusion of AM drugs on hospital formularies as well as coverage decisions by payers. Practice guidelines frequently provide additional information beyond the FDA-regulated labeling information and may include post-marketing data. Historically, the Infectious Diseases Society of America (IDSA) has typically considered updates to relevant guidelines every two years, after which those updates can take 8-12 years to implement. This means that novel AM drugs may not have been incorporated into clinical guidelines for many years after their approval, potentially limiting their appropriate uptake. However, IDSA recently published and then updated a less formal guidance document focused on treatment of specific antimicrobial-resistant pathogens, with a goal of providing actionable clinical guidance in a more timely way.[16] Ongoing monitoring will help characterize the impact of this guidance on the uptake of novel AM drugs. ERG's report also highlighted the need for readily available diagnostic tests to support clinical decision making and the appropriate use of novel AM drugs.

Hospital reimbursement challenges: In hospitals, Medicare and private payers frequently reimburse hospitals for the use of AM drugs through diagnosis-related groups (DRGs), which provide a fixed payment based on the patient's overall diagnosis. DRGs create an incentive to use the lowest cost, clinically acceptable drug, which in the case of antimicrobials is typically an older generic AM drug. For example, a 2018 analysis of pharmaceutical sales data showed that colistin, a low-cost generic AM drug that can have toxicity issues, was used more frequently than more expensive novel AM drugs that have shown better efficacy and fewer side effects.[17] Further, generic products typically have very low prices, and a recent analysis suggested that novel AM drug prices are dropping to the point of being only marginally higher than generic products.[18] In order to incentivize the appropriate use of novel AM drugs despite their relatively higher cost, the Centers for Medicare and Medicaid Services (CMS) have taken several actions recently to increase reimbursement to hospitals for novel AM drugs. Through the Inpatient Prospective Payment System (IPPS)[19], CMS increased New Technology Add-on Payments (NTAP)[iii] for certain AM drugs from 50 to 75 percent and increased payments to hospitals treating patients with resistant infections by updating their severity level designation, among other actions.[20] While HHS is monitoring the impact of these actions on the AM drug market, stakeholders have reported that NTAP is administratively burdensome for hospitals and may have little impact on hospital pharmacies' choice of AM drug.[21]

[iii] To be eligible for NTAP, 1) the technology must be new, generally defined as within two to three years following Food and Drug Administration (FDA) approval or market introduction; 2) if later than two to three years, the existing MS-DRG payment for the service involving the technology must be inadequate as demonstrated by meeting thresholds calculated annually by the CMS; and 3) the technology must be a substantial clinical improvement over existing services.

Collectively, these market challenges continue to strain the financial viability of companies that pursue novel AM drug development. As mentioned above, most development of AM drugs is currently done by small pharmaceutical companies. These companies typically have limited portfolios, often comprising only one or two drug candidates, and may have difficulty self-funding commercialization (including marketing and manufacturing) because they do not benefit from the infrastructure and economies of scale present within larger companies. Recently, several smaller companies have gone bankrupt or significantly restructured their activities after gaining FDA approval of novel AM drugs, citing the resource intensiveness of commercialization efforts and post-marketing studies.[22,23,24] These failures mean patients may not have access to these products despite significant public and private investment in their development, and promising products under development may be abandoned. Antibiotic product development expertise may also be lost as research and development teams are disbanded. These bankruptcies and reorganizations may deter other companies from initiating R&D for additional AM drugs,[25] leading overall to a potential underinvestment in new AM products by the commercial market compared to what may be societally optimal.

POLICIES TO ENCOURAGE NEW ANTIMICROBIAL DEVELOPMENT

To address many of the market challenges described in the previous section, HHS provides direct investments in research and development through the National Institute of Allergy and Infectious Diseases' support of basic, translational, and clinical research; CARB-X, a global public-private partnership dedicated to accelerating global antibacterial innovation, which is funded by NIH and ASPR/BARDA (among others); and ASPR/BARDA's late-stage funding of manufacturing, clinical trials, and regulatory activities. The U.S. Government also provides several incentives for product sponsors, most of which aim to reduce the upfront costs of drug development by speeding and streamlining FDA review. The Generating Antibiotic Incentives Now (GAIN) Act, passed as part of the Food and Drug Administration Safety and Innovation Act (2012, Public Law 112-144) allows certain AM drugs in development to be designated as Qualified Infectious Disease Products (QIDP), qualifying for fast track and priority review by the FDA.[26] As of September 2022, FDA had approved 29 new QIDPs for bacterial or fungal infections. The Limited Population Antibacterial Drug (LPAD) Pathway, created by the 21st Century Cures Act (2016, Public Law 114-255), can streamline the development of certain AM drugs designed to treat a serious or life-threatening infection in a limited population of patients with unmet needs,[27] which may reduce the costs of development. As of June 2021, FDA had approved two products under the LPAD pathway.[28]

Other existing incentives aim to create greater revenues for companies that develop new AM drugs. GAIN Act provisions provide QIDP-designated drugs with a five-year extension to any exclusivity that the application qualifies for upon approval. Using a hybrid approach, ASPR/BARDA has recently awarded contracts through Project BioShield to Paratek (sponsor of NUZYRA™) and VenatoRx (developer of cefepime-taniborbactam) for late stage development and potential purchase of these products for the Strategic National Stockpile.[29,30] The Project BioShield purchase of these products would provide revenue to their sponsors in addition to their revenue through the general pharmaceutical market.

BALANCING DRUG DEVELOPMENT AND STEWARDSHIP TO COMBAT RESISTANCE

The current U.S. market for pharmaceuticals links revenue with sales volume and pricing, such that companies must drive revenue increases through sales volume increases, price increases, or both. However, the link between revenue and sales volume can be a risk to goals of antimicrobial stewardship, which aims to minimize the development of antimicrobial resistance by using novel AM drugs sparingly and only when indicated by the needs of a particular patient. Revitalizing the AM drug pipeline depends on balancing the need for stewardship of novel AM drugs with the need for companies to receive sufficient return on investment to sustain their operations, support commercialization and marketing to ensure patient access, and complete post-marketing commitments including pediatric trials.

To counteract the market challenges described here and in ERG's results, and to support the principles of antibiotic stewardship, HHS has determined that a significant financial incentive outside of the current payment structure may be necessary. If such an incentive provides a guaranteed revenue stream, it could sustain the smaller companies currently engaged in antimicrobial research and development and encourage larger companies to re-enter this market. A recent analysis estimated that $200-250 million per product would likely sustain existing companies with AM drugs in the pipeline; larger awards of $1-2 billion may spur the development of additional products.[31]

The Fiscal Year 2024 President's Budget included a proposal to create a new payment mechanism to "delink" revenue from sales volume for AM drugs. Under this proposal, sponsors of selected products would be eligible to enter into contracts with HHS that would provide payments largely independent of the volume of product sales. Contracts would include stewardship, appropriate use, and patient access requirements, and the value of each contract would depend on desirable characteristics such as novel mechanism of action, novel active moiety, or retaining activity against multi-drug resistant pathogens. This proposal would provide a guaranteed revenue stream to AM drug sponsors who receive these contracts, regardless of how much product is used.

A considerable challenge to implementing such an incentive is how to appropriately value these products to determine the value of each contract and the overall cost of the incentive to the funder. Similar efforts underway in the United Kingdom could provide a model but are being implemented in a nationalized health system very distinct from that in the U.S.[32] Any significant financial incentive would need to be targeted to novel AM products that address a critical unmet need, including products that are most urgently needed to address an emerging pathogen, resistance to current antimicrobial products, or infections for which limited treatments are available. Characteristics such as a novel mechanism, novel active moiety, multiple indications, intravenous and oral formulations, relevance for special populations, or retaining activity against multi-drug resistant pathogens could also be used to evaluate products for this incentive. Importantly, any incentive would need to be paired with support for stewardship to ensure appropriate use.

NEXT STEPS

Additional research is needed to better understand the potential impact of the Fiscal Year 2024 budget proposal and other additional policy actions, such that any incentives are well designed and likely to achieve the goal of ensuring access to AM drugs now and into the future. Priority topics for

further research include ways of assessing the broader public health value of AM products as well as preventative strategies, and how to improve estimates of the health and economic burden of antimicrobial resistance to better understand the scope of the problem and therefore the need for new drugs.

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

ACKNOWLEDGEMENTS
The authors thank the HHS Project Advisory Group and the ASPE project team, which included Amber Jessup (now at the HHS Office of the Inspector General), Trinidad Beleche, Stephen Murphy, and Jessica Marus.

ABOUT THE AUTHORS
Casey Sullivan is a Social Science Analyst in the Office of Science and Data Policy in ASPE.
Allison Kolbe is a Health Science Policy Analyst in the Office of Science and Data Policy in ASPE.

SUGGESTED CITATION
Sullivan, C., & Kolbe, A. Understanding Markets for Antimicrobial Drugs. Washington, DC: Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services. April 2023.

_____

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

[1] CDC (2019). Antibiotic Resistance Threats in the United States, 2019. Available at: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.
[2] WHO (2020). Record number of countries contribute data revealing disturbing rates of antimicrobial resistance. Available at: https://www.who.int/news-room/detail/01-06-2020-record-number-of-countries-contribute-data-revealing-disturbing-rates-of-antimicrobial-resistance.
[3] CDC (2022). COVID-19: U.S. Impact on Antimicrobial Resisatance. Available at: https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf
[4] Sertkaya, A. et al. (2014). Analytical Framework for Examining the Value of Antibacterial Products. https://aspe.hhs.gov/reports/analytical-framework-examining-value-antibacterial-products-0
[5] World Health Organization (2021). 2021 Antibacterial agents in clinical and preclinical development. Available at: https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-gcp-irc/clinical-and-preclinical-database-infographics_2021.pdf
[6] National Strategy for Combating Antibiotic-Resistant Bacteria (2014). Available at. https://www.cdc.gov/drugresistance/us-activities/national-strategy.html
[7] Stritch, J. R., et al. (2020). Needs assessment for novel Gram-negative antibiotics in US hospitals: a retrospective cohort study. *Lancet Infectious Diseases*, 20(10) 1172-1181. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7272178/
[8] Kadri, S. S., et al. (2018). 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. Clinical Infectious Diseases, 67(12). Available at: https://academic.oup.com/cid/article/67/12/1803/5057528.
[9] Pei, S., et al. (2022). Challenges in forecasting antimicrobial resistance. *Emerging Infectious Diseases*, 29(4). Available at: https://wwwnc.cdc.gov/eid/article/29/4/22-1552_article
[10] CDC (2019). General information about *Candida auris*. Available at: https://www.cdc.gov/fungal/candida-auris/candida-auris-qanda.html
[11] Sertkaya, A., et al. (in preparation). State of Early-stage Antibacterial Drug Discovery: Time to Worry?
[12] Dheman, N. et al. (2021). An Analysis of Antibacterial Drug Development Trends in the United States, 1980–2019. *Clinical Infectious Diseases*, 73(11) e4444-e4450. Available at: https://academic.oup.com/cid/article/73/11/e4444/5862690
[13] Puzniak, L., Gupta, V., Yu, K., Ye, G., & Outterson, K. (2021). The impact of infections on reimbursement in 92 US hospitals, 2015-2018. *American Journal of Infection Control, 49*(10), 1275-1280. Available at: https://www.ajicjournal.org/article/S0196-6553(21)00202-9/fulltext
[14] Duke-Margolis Center for Health Policy (2020). Recommended Post-Market Incentive Strategies to Support the Development of Innovative Antibiotics. Available at: https://healthpolicy.duke.edu/publications/recommended-post-market-incentive-strategies-support-development-innovative.
[15] The New York Times (2022). Crisis Looms in Antibiotics as Drug Makers Go Bankrupt. Available at: https://www.nytimes.com/2019/12/25/health/antibiotics-new-resistance.html, last accessed February 24, 2022.
[16] Infectious Diseases Society of America (2022). IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Bacterial Infections: Version 2.0. Available at: https://www.idsociety.org/globalassets/idsa/practice-guidelines/amr-guidance/idsa-amr-guidance.pdf
[17] Alan Carr, Needham, November 5, 2018
[18] Madden, J., & Outterson, K. (2023). Trends in the global antibiotics market. *Nature Reviews Drug Discovery, 22*, 174. Available at: https://www.nature.com/articles/d41573-023-00029-5
[19] CMS (2019). 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). Available at:

https://www.cms.gov/newsroom/fact-sheets/fiscal-year-fy-2020-medicare-hospital-inpatient-prospective-payment-system-ipps-and-long-term-acute-0

[20] CMS (2020). Fact Sheet: Fiscal Year (FY) 2021 Medicare Hospital Inpatient Prospective Payment System (IPPS) and Long Term Acute Care Hospital (LTCH) Final Rule (CMS-1735-F). Available at: https://www.cms.gov/newsroom/fact-sheets/fiscal-year-fy-2021-medicare-hospital-inpatient-prospective-payment-system-ipps-and-long-term-acute-0

[21] Public Comment by Duke-Margolis Center for Health Policy on CMS-2019-0073-5348. Available at: https://www.regulations.gov/document?D=CMS-2019-0073-5348

[22] BioPharma Dive (2019). Achaogen files for bankruptcy protection, seeks asset sale. Available at: https://www.biopharmadive.com/news/achaogen-files-for-bankruptcy-protection-seeks-asset-sale/552737/.

[23] Reuters (2019). Antibiotics maker Melinta files for Chapter 11 bankruptcy. Available at: https://www.reuters.com/article/us-melinta-bankruptcy/antibiotics-maker-melinta-files-for-chapter-11-bankruptcy-idUSKBN1YV1AT,.

[24] GlobeNewswire (2020). La Jolla pharmaceutical company to acquire Tetraphase Pharmaceuticals, Inc. Available at: https://www.globenewswire.com/news-release/2020/06/24/2052639/0/en/La-Jolla-Pharmaceutical-Company-to-Acquire-Tetraphase-Pharmaceuticals-Inc.html

[25] STAT (2020). Antibiotics need a special place in the drug pricing debate. Available at: https://www.statnews.com/2020/01/07/antibiotics-need-a-special-place-in-the-drug-pricing-debate/

[26] FDA (2021). Final Guidance: Qualified Infectious Disease Product Designation Questions and Answers, FDA-2017-D-7001. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualified-infectious-disease-product-designation-questions-and-answers

[27] FDA (2020). Limited Population Pathway for Antibacterial and Antifungal Drugs – the LPAD Pathway. Available at: https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway

[28] GAO-22-195042 (2021). Drug development: Pathway for approving antibacterial and antifungal drugs for patients with limited treatment options is infrequently used. Available at: https://www.gao.gov/products/gao-22-105042

[29] HHS. New antibiotic purchased under Project BioShield to treat anthrax infections. Available at: https://www.medicalcountermeasures.gov/newsroom/2021/paratek/

[30] HHS (2022). HHS funds late-stage development, potential purchase of new antibiotic to combat a biothreat, treat antibiotic resistant infections. Available at: https://aspr.hhs.gov/newsroom/Pages/AMRantibiotics-Oct2022.aspx

[31] The MITRE Corporation (2019). Sustainable Biodefense Industrial Base for the Medical Countermeasures Enterprise, Antimicrobial Resistance Business Case.

[32] National Institute for Health and Care Excellence. Models for the evaluation and purchase of antimicrobials. Available at: https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials