

A Broken Antibiotic Market: Review of Strategies to Incentivize Drug Development

Sujata M. Bhavnani,¹ Kevin M. Krause,² and Paul G. Ambrose¹

¹Institute for Clinical Pharmacodynamics, Schenectady, New York, USA, ²San Francisco, California, USA

The threat posed by infections arising from antimicrobial-resistant bacteria is a global concern. Despite this trend, the future development of new antimicrobial agents is currently very uncertain. The lack of commercial success for newly launched antimicrobial agents provides little incentive to invest in the development of new agents. To address this crisis, a number of push and pull incentives have been constructed to support antimicrobial drug development. Push incentives, which are designed to lower the cost of developing new antimicrobial agents, include grants, contracts, public-private partnerships, tax credits, and clinical trial networks. Pull incentives, which are designed to facilitate higher financial returns for a newly launched antimicrobial agent, include those that decrease the time for a regulatory review, extend patent exclusivity, or provide premium pricing. Such incentives may also include direct, advanced, or milestone payments or they may be insurance-based whereby healthcare systems pay for the right to access an antimicrobial agent rather than the number of units administered. Another strategy involves the re-evaluation of interpretive criteria for in vitro susceptibility testing (susceptibility breakpoints) of old antimicrobial agents using the same standards applied to those of new agents, which will allow for an accurate determination of antimicrobial resistance. Although each of the above-described strategies will be important to ensure that antimicrobial agents are developed in the decades to come, the update of susceptibility breakpoints for old agents is a strategy that could be implemented quickly and one that could be the most effective for incentivizing drug developers and financiers to reconsider the development of antimicrobial agents.

Keywords. antimicrobial drug development; in vitro antimicrobial susceptibility test interpretative criteria; pull incentives; push incentives; susceptibility breakpoints.

THE PREVALENCE AND BURDEN OF ANTIMICROBIAL RESISTANCE

The threat posed by infections arising from antimicrobial-resistant bacteria and the need for new antimicrobial agents are a global concern as evidenced by the attention given to these issues by various national and international groups [1–5]. Although worldwide surveillance programs provide evidence of increasing rates of antimicrobial resistance, including rising numbers of multidrug and even pan-resistant isolates [6, 7], the challenge has been to estimate the burden of disease associated with infections due to antimicrobial-resistant bacteria.

In 2016, O'Neil [1] reported that >700 000 patients die due to infections caused by antimicrobial-resistant bacteria each year and predicted that this number would increase to 10

million by 2050, exceeding other causes of death including cancer, diabetes, diarrheal diseases, and automobile accidents. In a recent report from the United States (US) Centers for Disease Control and Prevention, the number of antibiotic-resistant infections occurring in the US alone was estimated to be more than 2.8 million per year. Of these infections, the number of deaths per year was estimated to exceed 35 000 [8]. The burden of antimicrobial resistance has also been evaluated. Cassini et al [9], using the 2015 data from the European Antimicrobial Resistance Surveillance Network, estimated 671 689 (95% uncertainty interval, 583 148 to 763 966) infections with antibiotic-resistant bacteria, 63.5% of which were associated with requiring healthcare. Of these cases, infection-attributable deaths were reported for 72.4% of patients and disability-adjusted life-years were estimated for 74.9% per every 100 000 individuals [9]. In addition to this disease burden, the economic impact of antimicrobial resistance is also profound, with an associated estimated cost to the US healthcare system of \$20 billion each year [10]. However, as described herein and in the companion paper by Ambrose et al [11], the prevalence of antimicrobial resistance is underestimated due to poor interpretive criteria for in vitro susceptibility testing (susceptibility breakpoints). Thus, the above-described burden is also likely underestimated.

Received 6 February 2020; editorial decision 17 February 2020; accepted 11 March 2020.

Correspondence: Sujata M. Bhavnani, PharmD, MS, IDSA, Institute for Clinical Pharmacodynamics, 242 Broadway, Suite 101, Schenectady, NY 12305 (sbhavnani@icpd.com).

Open Forum Infectious Diseases®

© The Author(s) 2020. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
DOI: 10.1093/ofid/ofaa083

THE BROKEN ANTIBIOTIC MARKET AND RECENT HISTORY

Despite the above-described data, the future development of new antibiotics, even for the treatment of patients with infections arising from multidrug-resistant pathogens, is currently very uncertain. To understand the basis for this uncertainty, it is important to understand changes in the landscape of antimicrobial drug development over the last several decades. In 2002, the US Food and Drug Administration (FDA) and European regulatory bodies presented proposals for Phase 3 clinical trial designs for antibacterial compounds, which included a noninferiority margin of 10%. Shortly thereafter, many large pharmaceutical companies, including Elly Lilly and Company and Bristol-Myers Squibb, ceased their antimicrobial drug discovery programs, at least in part as a reaction to this requirement [12]. The uncertainty of regulatory pathways, together with pipelines that included less novel agents and the limited opportunity for return on investment due to cost containment efforts in healthcare settings, including antimicrobial stewardship, further served to reduce interest in antimicrobial drug development.

In May 2012, Dr. Janet Woodcock of the FDA addressed the public health crisis of increasing antibiotic resistance and the inadequate development of new agents at an Expert Workshop on Facilitating Antibacterial Drug Development at the Brookings Institute. She acknowledged that the approach to change clinical trial designs for the development of antimicrobial agents taken by the agency in the last decade had contributed to the problem. Dr. Woodcock described the need for development pathways for antimicrobial agents focused on patients with unmet medical need [13]. A guidance document on antibacterial therapies for patients with unmet medical need, which was released a year later, outlined a pathway that included novel trial designs and smaller safety databases [14]. However, this guidance document and the release of subsequent updated guidance documents for other indications [15–18] have proven to be insufficient to renew the interest of the large pharmaceutical companies that divested their interest in the development of antimicrobial agents. This is in part because of the effects of antimicrobial stewardship on the commercial landscape for antimicrobial agents and because the pharma industry had refocused their pipelines on more financially lucrative therapeutic areas. In the case of antimicrobial stewardship, high-cost, narrowly differentiated agents are held in reserve and instead, low-cost competing alternatives are used. For those companies that did remain in the space, the clinical trial design requirements for unmet need limited the number of such patients available for study enrollment. In addition, most companies that remained focused on antimicrobial research and development (R&D) were small companies with limited resources that could not afford to build the commercial infrastructure necessary to bring new drugs to market and for which there was a diminishing opportunity for merger or acquisition-based exits. Finally, the

ongoing uncertainty regarding the regulatory path to approval for agents with a narrow spectrum of activity or that target the pathogens causing infections with greatest unmet medical need continue to discourage further drug development [19].

As larger companies lost interest in the space, mid-size and small pharmaceutical companies took their place. Some of the existing intellectual property and development expertise transferred from the larger to these smaller companies. For more than a decade, mid-size and smaller pharmaceutical and biotechnology companies have been working to develop antimicrobial agents with fewer resources. However, with reimbursement challenges and the questionable benefit of more expensive, narrowly differentiated agents (eg, products are only differentiated in that they have activity against a bacterial isolate possessing a clinically rare resistant determinant), the commercial success of newly launched antimicrobial agents has been minimal [20]. In addition, the lack of discovery research investment by large pharma and the inability of small companies to take on high-risk programs greatly diminished the number of companies exploring novel antimicrobial targets and classes of drugs. As a result, investor interest has further dwindled and the smaller companies that took up the challenge to develop new antimicrobial agents have been forced to merge or sell their assets for less than the cost expended to develop the product. Such was the case for Achaogen, a company that filed for bankruptcy in April 2019 [21]. Achaogen launched plazomicin in July 2018. The company reported just \$800 000 in total sales for 2018 [22] and filed for bankruptcy in April 2019 [21]. In June, 2019 Cipla USA, Inc. agreed to buy the worldwide rights, excluding Greater China, to plazomicin for \$4 650 000 (plus certain cash and noncash considerations totaling \$10 500 000 and assumption of certain contract liabilities) [23]. These events unfolded in less than 1 year, even though the drug was developed to address the unmet medical need of patients with a range of antimicrobial-resistant organisms, including carbapenem-resistant Enterobacteriaceae, and was expected to reach \$500 million in sales annually [24]. This program was funded in part by a \$124.4 million contract with the Biomedical Advanced Research and Development Authority ([BARDA], which is part of the Office of the Assistant Secretary for Preparedness and Response in the US Department of Health and Human Services) [25].

In the case of meropenem-vaborbactam, which was approved by the FDA in 2017 for the treatment of adult patients with complicated urinary tract infections, including pyelonephritis, caused by designated susceptible Enterobacteriaceae, *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* species complex, up to a \$90 million award was provided by BARDA [26]. However, Melinta Therapeutics, which markets this agent, reported total cumulative sales from launch in 2017 through to November 2019 that were only \$20.6 million [20]. These sales figures led to a filing by Melinta Therapeutics

in November 2019 that highlighted concerns about their ability to continue company operations if their debt could not be restructured or a suitor to acquire the company could not be found [27]. Unfortunately, this filing was followed by filing for Chapter 11 bankruptcy in December 2019 [28]. In partnership with Deerfield Management Company, L.P., Melinta recently emerged from Chapter 11 [29]. Despite the outcome for both companies, these 2 examples highlight that there have been some small companies still willing to invest in the space. However, the sales of the products and the resulting valuations applied to these assets do not reflect the life-saving role they play for patients. Unfortunately, these examples are not unique because other recent launches of agents for the treatment of patients with infections arising from antimicrobial-resistant bacteria have led to minimal sales relative to the investment made. Three companies that launched antimicrobial agents after plazomicin reported sales that were dwarfed by the operational expenses of keeping these agents on the market. Such expenses include postapproval regulatory commitments, pharmacovigilance, development of automated antimicrobial susceptibility testing, ongoing drug manufacturing, medical affairs, and sales and marketing [30]. The products include Paratek's omadacycline (\$3.1 million sales on a \$32.6 million loss in Q3 2019) [31], Tetrphase's eravacycline (\$1.0 million sales on a \$16.3 million loss in Q3 2019) [32], and Nabriva's lefamulin (\$1.4 million sales on a \$17.8 million loss in the first partial quarter [Q3 2019] postapproval) [33]. Recently, Tetrphase announced the sale of the company to AcelRX, a non-infectious diseases company, in March 2020. Included in the sale was eravacycline, which achieved \$3.3 million in sales in 2019 following approval by the FDA in August 2018. The reported sale price of the company was \$14.4 million, paid in stock in the acquiring company, plus the potential of up to an additional \$12.5 million if sales targets are met. This valuation is in stark contrast to Tetrphase's peak market capitalization of \$1.8 billion in 2015 (a valuation which based on the expectation of an oral outpatient treatment) and the approximately \$600 million raised to date for the company. In fact, the value of Tetrphase in this transaction was very near the expected cash on hand, which effectively put no value on their approved product [34, 35]. Given the above, it is clear to see that the antibiotic market is broken.

STRATEGIES TO INCENTIVIZE ANTIMICROBIAL DRUG DEVELOPMENT

The above-described lack of commercial successes for newly launched antimicrobial agents provides little incentive to develop such drugs. As a result, the current landscape is one with little-to-no investor interest and drug discovery, limited pipelines, and a staggering loss of institutional knowledge and expertise, with the exodus of scientists from this field due to the lack of employment opportunities. To address this crisis,

various incentives, as described below, have been constructed to support antimicrobial drug development.

Push incentives are designed to lower the cost of discovering and developing new antimicrobial agents. Such incentives take the form of grants, contracts, public-private partnerships, tax credits, and clinical trial networks. The premise for these incentives is that by promoting basic research, the resulting data can be leveraged commercially to address public health priorities. Because this funding mechanism is at risk if the asset fails during development, developers may feel pressure to take a more optimistic view of the data and dismiss important signals to stop a program in order to continue a given funding stream [36–38]. However, these risks are mitigated through close coordination between the company and the funding partner and by using expense reimbursement contracts. Funding partners include Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the US Department of Defense, the National Institutes of Health and National Institute of Allergy and Infectious Diseases, the Global Antibiotic Research and Development Partnership, the Wellcome Trust, the Bill & Melinda Gates Foundation, BARDA, the Innovative Medicines Initiative (IMI), and the REPAIR Impact Fund.

CARB-X is currently investing \$500 million over the period from 2016 to 2021 to accelerate the development of innovative antimicrobial agents and other therapeutics, vaccines, and rapid diagnostics to address drug-resistant bacterial infections [39]. CARB-X funding allows recipients to get investigational antimicrobial agents from preclinical development through to the filing of the investigational new drug application. BARDA, which was established by the US Congress to provide federal investments, provides support for investigational antimicrobial agents in later stage development and serves to bridge the gap after a CARB-X award ends. IMI in Europe fulfills a similar function.

Pull incentives, which impact revenue generated after regulatory approval, can be grouped into 2 categories: lego-regulatory and outcome-based incentives. Lego-regulatory pull incentives are those that indirectly facilitate higher market returns for a newly launched antimicrobial agent. Such incentives may include those that decrease the time for a regulatory review, extend patent exclusivity, or provide premium pricing. Outcome-based incentives include direct, advanced, or milestone payments [36–38]. Because pull incentives reward successful R&D programs, and the incentive is received at the point of or after regulatory approval or market entry, the developer assumes the majority of the risks. Thus, pull incentives may not be immediately meaningful for earlier stage companies that may lack the resources to transition assets to late-stage development or regulatory approval. In addition, pull incentives take a long time to implement with uncertain outcomes.

The GAIN (Generating Antibiotic Incentives Now) Legislation, which was passed by the US Congress in 2012, is an example of a lego-regulatory pull incentive. This legislation allows for fast track and priority review status for drugs that target qualifying pathogens and, if approved, extends market exclusivity by an additional 5 years (in addition to the existing 5 years). Designed for expediting the approval of qualified infectious disease products (QIDPs), 15 different drugs have gained a QIPD designation status and have been subsequently approved by the FDA since the GAIN Act was passed [40, 41]. However, although agents approved are deemed to provide value, commercial success for such agents is yet to be realized. In fact, much of the current pipeline of newer agents is at risk for being unable to remain on the market in part because of a generally narrow product differentiation. Reducing the cost of antimicrobial development through streamlined pathways is likely to be helpful [42], but it will not be sufficient to overcome the narrow product differentiation and the impact of antimicrobial stewardship.

Pull incentives may also be insurance-based whereby health-care systems pay for the right to access an antimicrobial agent rather than the number of units administered. To this end, the Medicare Hospital Inpatient Prospective Payment System has proposed to increase New Technology Add-On Payments (NTAP) to 75% from 50% for all new antibiotics designated as QIDP by the FDA [43, 44]. However, given the premise for antimicrobial stewardship programs, which is to use antimicrobial agents optimally, this will not be sufficient to incentivize antimicrobial drug development. In addition, the mechanics of the NTAP system have proven to be a barrier to use at the local hospital due to the associated paperwork burden, the reliance on pharmacists to submit an NTAP application, that the money flows back in a topline manner to the hospital rather than directly to the pharmacy budget, the difficulty with NTAP reimbursement tracking because they are not coded to individual drugs but rather are provided as bundled payments across all NTAP qualified drugs, and that even 75% reimbursement still prices many newer drugs well above the cost of generics. When one considers the cost for a company to effectively launch a new antimicrobial agent, such an upfront investment cannot be recouped, even after several years on the market. The Infectious Disease Society of America (IDSA) and others have called on the Center for Medicine & Medicaid Services for an improved Medicare reimbursement strategy for antimicrobial agents [45]. The IDSA proposal strikes a balance between patient-centered care and drug developer needs. The proposal is patient-centered and allows a positive return on the investment associated with antimicrobial R&D.

The IDSA proposal requires hospitals to implement antimicrobial stewardship programs that are consistent with US Centers for Disease Control and Prevention recommendations. The proposal encourages patient-centered new and appropriate

antimicrobial agent use through antimicrobial stewardship programs while generating antimicrobial agent use and resistance pattern data to support future stewardship decision making. The proposal allows a positive return to drug manufacturers by decoupling the cost of new antimicrobial agents from the standard Medicare Diagnosis-Related Group payment. The ultimate goal of the IDSA proposal is to improve patient care by improving current and future antimicrobial stewardship practices while stabilizing the antibiotic marketplace.

Another strategy that merits serious discussion involves the re-evaluation of susceptibility breakpoints of old antimicrobial agents using the same standards applied to that of new agents. Like that suggested by the IDSA, this proposal is also patient-centered and allows for a positive return on the investment for drug developers. A scientifically justified adjustment in the susceptibility breakpoints of old antimicrobial agents that is consistent with modern standards will aid antimicrobial stewardship efforts for new and old agents alike. In particular, changes to susceptibility breakpoints for older antimicrobial agents can help with the effort to clearly characterize the prevalence of antimicrobial resistance and better identify patients receiving legacy antimicrobial agents who are at risk for clinical failure. Such information will in turn help define the role of new antimicrobial agents. The implementation of this proposal will also improve patient safety. As illustrated by the example of amikacin and plazomicin against Enterobacteriaceae in the companion paper by Ambrose et al [11], the impact of such changes can dramatically affect the number of isolates that would be categorized as amikacin-resistant and thus, better define when plazomicin might be a better choice amongst the aminoglycosides.

United States Antimicrobial Susceptibility Test (USCAST) committee members recently reviewed how susceptibility breakpoints for old antimicrobial agents were determined and how their adjustment can impact the perceived utility of an old relative to a new antimicrobial agent. In addition, they described the data and analysis needs to systematically re-evaluate susceptibility breakpoints for old antimicrobial agents [11]. Using such a process, this group has undertaken the review of susceptibility breakpoints for older antimicrobial agents, including the fluoroquinolones and aminoglycosides [46, 47]. There are many important benefits that could be realized by the implementation of corrected susceptibility breakpoints. The reliable prediction of the efficacy of potential antimicrobial dosing regimens based on the use of corrected susceptibility breakpoints will allow for the optimization of antimicrobial therapy for individual patients. This is essentially the goal of antimicrobial stewardship activities. Correction of the susceptibility breakpoints for old agents will allow for the characterization of antimicrobial resistance for old and new agents based on the same criteria. An accurate characterization of antimicrobial resistance will allow for a better understanding of the pathogens and associated infections for which new antimicrobial agents are needed. Because

antimicrobial resistance has been underestimated to date due to poor susceptibility breakpoints, the commercial benefit of new agents for certain patient populations will be more apparent, which, in turn, should reincentivize drug development.

CONCLUSIONS

Herein, various push and pull incentives to stimulate antimicrobial drug development are described. Although all of these strategies will be important to ensure that antimicrobial agents are developed in the decades to come, the correction of susceptibility breakpoints for old agents is a strategy that could be implemented quickly, and one that could be the most effective for incentivizing drug developers and financiers to reconsider the development of antimicrobial agents. However, even with the promise of all of these strategies, including corrected susceptibility breakpoints, it is important to consider the societal need for antimicrobial agents, one that cannot be accurately reflected by current or improved financial models. As recently suggested by Rex and Outtersen [48], antibiotics represent a valuable form of insurance, given that these agents resemble the “fire departments” or “fire extinguishers” of medicine. Like fire-fighting infrastructure, antimicrobial drug development must be protected and fostered in advance of the need of such agents.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

- O'Neil J. Tackling drug-resistant infections globally: Final report and recommendations. May, 2016. Available at: http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf. Accessed 6 February 2020.
- Access to Medicine Foundation. Antimicrobial resistance benchmark 2018. January, 2018. Available at: <https://accessmedicinefoundation.org/media/atmf/2017-Methodology-for-2018-Antimicrobial-Resistance-Benchmark.pdf>. Accessed 6 February 2020.
- Ardal C, Carmeli Y, Ciabuschi F, et al. Drive-AB Report. Revitalizing the antibiotic pipeline, stimulating innovation while driving sustainable use and global access. January, 2018. Available at: <http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf>. Accessed 6 February 2020.
- World Health Organization, Global Observatory on Health R&D. Antibacterial products in clinical development for priority pathogens. November, 2018. Available at: https://www.who.int/research-observatory/monitoring/processes/antibacterial_products/en/. Accessed 6 February 2020.
- Intragency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. Summary of recommendations and key messages. Report to the Secretary-General of the United Nations. April, 2019. Available at: https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_summary_EN.pdf?ua=1. Accessed 6 February 2020.
- Castanheira M, Deshpande LM, Mendes RE, et al. Variations in the occurrence of resistance phenotypes and carbapenemase genes among Enterobacteriaceae isolates in 20 years of the SENTRY Antimicrobial Surveillance Program. *Open Forum Infect Dis* 2019; 6:(Suppl 1):S23–33.
- Gales AC, Seifert H, Gur D, et al. Antimicrobial susceptibility of *Acinetobacter calcoaceticus* - *Acinetobacter baumannii* complex and *Stenotrophomonas maltophilia* clinical isolates: results from the SENTRY antimicrobial surveillance program (1997–2016). *Open Forum Infect Dis* 2019; 6:(Suppl 1):S34–46.
- U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Available at: <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>. Accessed 6 February 2020.

- Cassini A, Högberg LD, Plachouras D, et al, Burden of AMR Collaborative Group. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European economic area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2018; 19:56–66.
- Smith R, Coast J. The true cost of antimicrobial resistance. *BMJ* 2013; 346:1–5.
- Ambrose PG, Bhavnani SM, Andes DR, et al. Old in vitro antimicrobial breakpoints are misleading stewardship efforts, delaying adoption of innovative therapies, and harming patients. *Open Forum Infect Dis* 2020; 7(7).
- Shlaes DM, Moellering RC Jr. The United States Food and Drug Administration and the end of antibiotics. *Clin Infect Dis* 2002; 34:420–2.
- Shlaes DM, Sahn D, Opiela C, Spellberg B. The FDA reboot of antibiotic development. *Antimicrob Agents Chemother* 2013; 57:4605–7.
- United States Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases. Silver Spring, MD: United States Department of Health and Human Services, Food and Drug Administration, August 2017:1–19. Available at: <https://www.fda.gov/media/86250/download>. Accessed 6 February 2020.
- United States Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. Silver Spring, MD: United States Department of Health and Human Services, Food and Drug Administration, October 2013:1–18. Available at: <https://www.fda.gov/media/71052/download>. Accessed 6 February 2020.
- United States Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment. Draft Guidance. Silver Spring, MD: United States Department of Health and Human Services, Food and Drug Administration, January 2014:1–23. Available at: <https://www.fda.gov/media/75149/download>. Accessed 6 February 2020.
- United States Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. Draft Guidance. Silver Spring, MD: United States Department of Health and Human Services, Food and Drug Administration, May 2014:1–19. Available at: <https://www.fda.gov/media/79516/download>. Accessed 6 February 2020.
- United States Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Complicated Urinary Tract Infections: Developing Drugs for Treatment. Silver Spring, MD: United States Department of Health and Human Services, Food and Drug Administration, June 2018:1–19. Available at: <https://www.fda.gov/files/drugs/published/Complicated-Urinary-Tract-Infections---Developing-Drugs-for-Treatment.pdf>. Accessed 6 February 2020.
- United States Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Limited Population Pathway for Antibacterial and Antifungal Drugs. Draft Guidance. Silver Spring, MD: United States Department of Health and Human Services, Food and Drug Administration, June 2018:1–14. Available at: <https://www.fda.gov/media/113729/download>. Accessed 6 February 2020.
- Needham & Company, LLC. Antibiotic and Antifungal Update: January 2020. Research Report. January 28, 2020. Available at: <https://needham.bluematrix.com/sellside/EmailDocViewer?encrypt=7af51ecf-56b6-4827-bd16-3186a8db8715&mime=pdf&co=needham&id=8&source=mail>. Accessed 6 February 2020.
- Achaogen, Inc. Press release. April 15, 2019. Achaogen plans for near-term sale using structured process through Chapter 11 of the U.S. bankruptcy code. *globeNewswire*. Available at: <https://www.globenewswire.com/news-release/2019/04/15/1803906/0/en/Achaogen-Plans-for-Near-Term-Sale-Using-Structured-Process-Through-Chapter-11-of-the-U-S-Bankruptcy-Code.html>. Accessed 6 February 2020.
- Achaogen, Inc. Press release. March 28, 2019. Achaogen reports fourth quarter and full year 2018 financial results and provides corporate update. Available at: <http://www.globenewswire.com/news-release/2019/03/28/1783626/0/en/Achaogen-Reports-Fourth-Quarter-and-Full-Year-2018-Financial-Results-and-Provides-Corporate-Update.html>. Accessed 6 February 2020.
- In the United States Bankruptcy Court for the District of Delaware v. Achaogen, Inc.* Chapter 11. Case No. 19-10844 (BLS). Docket #0295. June 22, 2019. Available at: <http://www.kccllc.net/achaogen/document/191084419062200000000000>. Accessed 6 February 2020.
- Carroll J. Once picked as a \$500M winner, bankrupt Achaogen auctions off its antibiotic for a fraction of that. *Endpoint News*. June 7, 2019. Available at: <https://endpts.com/once-picked-as-a-500m-winner-bankrupt-achaogen-auctions-off-its-antibiotic-for-a-fraction-of-that/>. Accessed 6 February 2020.
- Achaogen Inc., April 1, 2019. United States Securities and Exchange Commission Filing. Form 10-K. Available at: <https://seekingalpha.com/filing/4427413>. Accessed 6 February 2020.

26. The Medicines Company. October 1, 2015. The Medicines Company announces BARDA exercises next option on contract for support of the development of CARBAVANCE® (meropenem/RPX7009) for Drug-Resistant Gram-Negative Pathogens. Available at: <https://www.themedicinescompany.com/investor/pr/1522911/>. Accessed 6 February 2020.
27. Melinta Therapeutics, Form 10-Q. November 12, 2019. Available at: <http://ir.melinta.com/static-files/68f17e49-004a-4965-b17f-53982e3e7d85>. Accessed 6 February 2020.
28. Melinta Therapeutics, Press release. December 27, 2019. Melinta Therapeutics announces restructuring support agreement with its secured lenders under its senior credit facility. Available at: <http://ir.melinta.com/news-releases/news-release-details/melinta-therapeutics-announces-restructuring-support-agreement>. Accessed 6 February 2020.
29. Melinta Therapeutics. Press release. April 20, 2020. Melinta Therapeutics successfully completes financial restructuring. Available at: <http://ir.melinta.com/news-releases/news-release-details/melinta-therapeutics-successfully-completes-financial>. Accessed 15 May 2020.
30. Cirz R, Krause K, Lichtenstein C, Wagenaar R. Antibiotic Bootcamps for Developers: Post-Approval Economics for New Antibiotics. ASM/ESCMID Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance, Boston, MA, September 3-6, 2019. <https://carb-x.org/resource/bootcamp-post-approval-economics-for-new-antibiotics-asm-escmid-2019/>. Accessed 6 February 2020.
31. Paratek Pharmaceuticals, News release. November 12, 2019. Paratek Pharmaceuticals generates net revenues of \$3.9 million in the third quarter of 2019. Available at: <https://investor.paratekpharma.com/news-releases/news-release-details/paratek-pharmaceuticals-generates-net-revenues-39-million-third>. Accessed 6 February 2020.
32. Tetrphase Pharmaceuticals, Press release. November 12, 2019. Tetrphase Pharmaceuticals reports third quarter 2019 financial results and highlights recent corporate developments. Available at: <https://ir.tphase.com/news-releases/news-release-details/tetrphase-pharmaceuticals-reports-third-quarter-2019-financial>. Accessed 6 February 2020.
33. Nabriva Therapeutics, Press release. November 12, 2019. Nabriva Therapeutics reports third quarter 2019 financial results and recent corporate highlights. Available at: <http://investors.nabriva.com/news-releases/news-release-details/nabriva-therapeutics-reports-third-quarter-2019-financial>. Accessed 6 February 2020.
34. Tetrphase Pharmaceuticals, Inc., United States securities and exchange commission filing. Form 8-K, March 15, 2020. Available at: <https://sec.report/Document/0001193125-20-073898/>. Accessed 2 April 2020
35. Rex J, Outterson K. Tetrphase Sold for \$14m... And \$600m goes up in smoke! March 23, 2020. Available at: <https://amr.solutions/2020/03/23/tetrphase-sold-for-14m-and-600m-goes-up-in-smoke/>. Accessed 2 April 2020.
36. Renwick MJ, Brogan DM, Mossialos E. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *J Antibiot (Tokyo)* **2016**; 69:73–88.
37. Kozak ML, Larsen JC. Economic incentives for antibacterial drug development: alternative market structures to promote innovation. In: *Antimicrobial Resistance in the 21st Century*. Fong I, Shlaes D, Drlica K, eds. 2nd ed. New York: Springer; **2018**.
38. Antimicrobial Resistance Tackling the Gap in R&D Resources with Pull Incentives - in collaboration with Wellcome. World Economic Forum. May 2018. Published June 22, 2018. Available at: <https://www.weforum.org/reports/antimicrobial-resistance-tackling-the-gap-in-r-d-resources-with-pull-incentives-in-collaboration-with-wellcome-trust>. Accessed 6 February 2020.
39. CARB-X Combating Antibiotic Resistant Bacteria. Funding partners. Available at: <https://carb-x.org/partners/funding-partners/>. Accessed 6 February 2020.
40. Slater J. July 2019. QIDP: What have we GAINed. White paper. Pharma Intelligence Informa. Available at: <https://pharmaintelligence.informa.com/-/media/informa-shop-window/pharma/2019/files/article-packs/qidp---what-have-we-gained-whitepaper.pdf>. Accessed 6 February 2020.
41. FDA News Release. August 19, 2019. FDA approves new antibiotic to treat community-acquired bacterial pneumonia. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-treat-community-acquired-bacterial-pneumonia>. Accessed 6 February 2020.
42. Ambrose PG. Antibiotic bill doesn't GAIN enough ground. *Nat Med* **2011**; 17:721–22.
43. Verma S. August 6, 2019. Securing access to life-saving antimicrobial drugs for American seniors. Available at: <https://www.cms.gov/blog/securing-access-life-saving-antimicrobial-drugs-american-seniors>. Accessed 6 February 2020.
44. Dall C. August 5, 2019. Medicare payment changes aim to boost antibiotic development. Available at: <http://www.cidrap.umn.edu/news-perspective/2019/08/medicare-payment-changes-aim-boost-antibiotic-development>. Accessed 6 February 2020.
45. Sears C. Infectious Diseases Society of America. Letter to Verma Seema, Centers for Medicare and Medicaid Services. June 24, 2019. Available at: https://www.idsociety.org/globalassets/idsa/policy--advocacy/current_topics_and_issues/access_and_reimbursement/2019/062419-idsa-letter-to-cms-re-ipp.pdf. Accessed 6 February 2020.
46. USCAST, the National Antimicrobial Susceptibility Testing Committee for the United States. Quinolone *in vitro* susceptibility test interpretive criteria evaluations. Version 1.3, October 15, 2018. Available at: <https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg>. Accessed 6 February 2020.
47. USCAST, the National Antimicrobial Susceptibility Testing Committee for the United States. Aminoglycoside *in vitro* susceptibility test interpretive criteria evaluations. Version 1.3, February 24, 2019. Available at: <https://app.box.com/s/zcjr3jv5dacwop8cnj87gnf03o9qfy>. Accessed 6 February 2020.
48. Rex JH, Outterson K. Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach. *Lancet Infect Dis* **2016**; 16:500–5.