

Recommended Post-Market Incentive Strategies to Support the Development of Innovative Antibiotics

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Introduction

Combating the growing threat of antimicrobial resistance (AMR) requires generation of innovative antibiotics, but a low expected return on investment limits commercial development. Existing incentives have not adequately addressed the financial challenges developers encounter. Reviving investment and development in this space will require new approaches that create a sustainable market for antibiotic products.

New antibiotics struggle to generate financial returns for several reasons. First, hospital antibiotic stewardship programs restrict the use of newer antibiotics to cases where there are few or no other treatment options.¹ Because unit-sales generate revenue under current fee-for-service (FFS) payment schemes, stewardship limits revenue. Second, regulatory approvals based on noninferiority trials do not provide comparative effectiveness evidence to justify rapid adoption of new antibiotics or enhanced reimbursement for innovative characteristics.² Widespread adoption is delayed until data regarding new antibiotics' effectiveness and susceptibility to resistance is collected and disseminated. Third, rising reimbursement pressures and constrained hospital budgets encourage providers to first prescribe the least expensive therapeutic option. New antibiotics are usually more expensive, which may reduce their frequency of use. Because new antibiotics face these persistent challenges, post-market incentives are needed to sustain antibiotic research and the development pipeline.

Over the past year and a half, with support from the Wellcome Trust, the Duke-Margolis Center for Health Policy has convened experts from across the AMR landscape to develop domestic policy approaches and identify opportunities for global coordination of promising market incentives.³ Duke-Margolis advanced these multi-stakeholder conversations and collected key considerations underpinning three primary goals: (1) advancing technical details for incentive models in the context of the US market; (2) identifying broader options to support the sustainability of large post-market incentives; and (3) supporting the development of principles and approaches for global coordination.

This report describes promising existing or proposed post-market incentives, limitations to incentive approaches, and opportunities to facilitate incentive implementation. Recommendations and needed next steps are identified throughout the report and are summarized in the conclusions. Policymakers must engage collaboratively to implement a spectrum of incentives that bolster new antibiotic development, stewardship, and access. Actions that enhance multilateral policy alignment, encourage collaboration, and yield additive benefits are of particular importance. And while new incentive approaches have varying levels of feasibility, taking incremental actions will build a trajectory for a more sustainable path to addressing AMR.

Promising Steps to Reinvigorate the Market for Antibiotics

Reinvigorating the market for antibiotics requires action immediately, but the most impactful changes may not be feasibly implemented in the short-term. As a result, the spectrum of needed incentives must be considered in the context of time and complexity to implementation; some incentives might be limited in impact, but can be put into action quickly and provide immediate relief. The following discussion categorically details incentives that are needed to fully address the antibiotic market challenges, categorized by the steps that need to be taken in the short-, medium- and long-term. Intermediate steps typically require additional time to leverage expanded administrative authorities or new appropriations, and longer-term steps involve consensus-building to extensively align the priorities of multiple stakeholders.

Short-Term Steps

Needed short-term steps are expedient and signal support for the antibiotic market, but may be limited in impact if implemented as standalone solutions. Nonetheless, these approaches may build a foundation for future actions. Many stakeholders view increased reimbursement for antibiotics as the most effective action to avoid further deterioration of new antibiotic development. The most significant action to-date has been by the Centers for Medicare and Medicaid Services (CMS) through the fiscal year (FY) 2020 Inpatient Prospective Payment System (IPPS).

CMS used a limited set of rule-making authorities to increase hospital reimbursement for new antibiotics. CMS's final FY 2020 IPPS rule made adjustments to ease antibiotic adoption during initial years on the market through three key changes.⁴ First, CMS increased reimbursement through the New Technology Add-On Payment (NTAP) program.⁵ The NTAP program provides up to 65% of the cost of an innovative drug or device that exceeds a diagnosis-related group (DRG)-based reimbursement. For qualifying antibiotics, CMS will increase the amount to 75% of the excess costs. Second, CMS waived one of three criteria used to determine which products qualify for the NTAP program—innovative antibiotics no longer need to demonstrate substantial clinical improvement over existing treatments.² Because antibiotics are generally approved based on non-inferiority trials, substantial clinical improvement is particularly hard to demonstrate before a product is more widely used. Finally, CMS changed the severity score for eighteen antibiotic-resistant infections, providing increased reimbursements that reflect the increased costs associated with treating resistant infections.

CMS has signaled their intention to build on these changes in subsequent years, and the draft FY2021 IPPS rule outlines two new adjustments for antibiotics.⁶ The first is to allow products that were approved through the Limited Population Pathway for Antibacterial Development (LPAD) to qualify for the FY2020 NTAP modifications. Second, CMS will allow for conditional

approval of antibiotic products that qualify for NTAP, but that miss the deadline for inclusion in the final rule due to timing of approval. This change would enable these antibiotic products to receive NTAP reimbursements sooner.

Intermediate Steps

Intermediate steps require additional time to implement because they go beyond the administrative authority of individual government agencies, require Congressional appropriations, or depend on a common understanding of antibiotic value or product eligibility. While not immediate, intermediate steps are additive, can be implemented relatively quickly, and are fundamental to progressive improvement.

The Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act provides a mechanism to reimburse antibiotics independently of Medicare's DRG-based bundled payments. DISARM was initially introduced in Congress in 2015.⁷ The most recent version of this proposal was reintroduced within a version of the CARES Act (S. 3548) but was subsequently removed before that bill became law (H.R. 748, now Public Law 116-136).⁸⁻¹⁰ If enacted in future legislation, hospitals would be reimbursed for qualified antibiotics (including all Qualified Infectious Disease Products) based on their average sales price (ASP).^{11,12} Like an increased NTAP, DISARM would mitigate the financial impact on hospital pharmacies that procure and dispense innovative antibiotics, potentially speeding inclusion of qualified antibiotics on hospital formularies.

Complementing CMS-led incentives, BARDA has existing contracting mechanisms that might be expanded to support antibiotic development and early commercialization over the next several years. In 2020, BARDA will begin funding the late-stage development, post-marketing requirements, and initial procurement of an antibiotic for the treatment of anthrax through a Project BioShield contract with Paratek Pharmaceuticals.¹³ This mechanism is a pull incentive with extension options if milestones are achieved. While BARDA has invested non-dilutive funding into pre-clinical and early clinical development through CARB-X and public-private partnerships (through its Other Transaction Authority), this new contracting mechanism addresses the financial post-approval commercialization challenges that antibiotic developers face.¹⁴ This payment mechanism builds toward paying for anticipated value of the antibiotic for society, rather than reimbursing on a per-use basis. With additional authorities and money granted through Congress, this program could be expanded and applied to a broader set of high priority antibiotic products. Due to the ongoing SARS-CoV-2 pandemic, BARDA has received additional funds to set up these types of contracts to support post-market operations for needed infectious disease therapeutics, vaccines, and diagnostics.¹⁵ These contracts might serve as an example for developing similar antibiotic-focused arrangements.

Longer-Term Steps

Reinvigorating the market for antibiotics depends on implementing incentives that meaningfully restructure how antibiotics are reimbursed. Steps to implementation of these incentives are longer-term because they are more complex, but can align multiple stakeholder priorities. Ultimately, taking these steps can simultaneously support the development of innovative antibiotics, reimbursement based on value, antibiotic stewardship programs, and value-based healthcare. Successful execution of longer-term steps is achieved through continued progress on the short-term and intermediate steps that support improved reimbursement for AMR products and better evidence generation.

Several global organizations have identified market entry rewards (MERs) as a promising incentive for novel antibiotic development and access.^{16–18} MERs are large payments to developers following the approval of an antibiotic with defined characteristics and can vary in size or time according to additional product criteria or developer obligations. MERs of great enough magnitude might attract both small and large developers to re-enter the antibiotics space and drive additional investments in antibiotic research and development. However, MERs do not necessarily align stakeholders around additional priorities including appropriate antibiotic stewardship and enhanced data collection. Furthermore, multiple organizations have estimated effective MERs would need to offer developers at least \$1 billion, jeopardizing their financial and political feasibility.^{16,17} Coordinating public sector resources from multiple countries to fund and pilot a MER, or reframing reward distribution through contracts or population-based payments, have the potential to overcome financial and political barriers.

Population-based payments are another incentive option that Duke-Margolis and other organizations have recommended for their potential to simultaneously improve antibiotic development, payment, and stewardship.^{19–21} As a central tenant, such population-based models, like subscription payments, recognize that antibiotics provide value beyond that reflected by the inexpensive prices the market currently demands.

Population-based payment models align the priorities of multiple stakeholders. Developers realize more predictable revenue, which might encourage new investments in antibiotic research and development. Specific eligibility criteria can direct reimbursement to high priority areas of unmet need. And to better understand the value of new antibiotics, payers might require participating developers to contribute to the collection of data on product utilization and patient outcomes. This additional data can then be used to support appropriate antibiotic prescribing, as well as potential label expansions. Population-based models can also be tailored to address the needs of a given population.

Already, the United Kingdom (UK) is piloting a subscription arrangement that delinks antibiotic revenue from volume use by evaluating antibiotic qualities that contribute to population health.²² The UK's initial evaluation framework incorporates a Health Technology Assessment (HTA) report with modeling and expert judgement.²³ The antibiotic qualities that go beyond traditional clinical impacts include diversity, transmission, enablement, spectrum, and insurance values (see the EEPRU report Framework for Value Assessment of New Antimicrobials for detailed descriptions).²⁴ The UK's pilot will initially be tested with two antibiotics, but several years remain until the contracting model is implemented. The entire process will be closely monitored for potential application in other countries.

In Sweden, the Public Health Agency has developed a value-based insurance model that guarantees developers a certain level of revenue from the government regardless of the volume of an antibiotic used.²⁵ In Sweden, resistance rates are low, so new antibiotics are rarely needed. But to ensure preparedness, the country wants novel drugs to be accessible. The purpose of the model is to encourage developers to enter the Swedish market and to ensure availability when needed. This model partially delinks antibiotic revenue from volume used.

Within the US context, the Duke-Margolis subscription payment framework outlines a population-based payment model that provides a recurring payment to antibiotic developers in exchange for reliable availability of an antibiotic. A recurring payment would be negotiated by a third-party priority antibiotic manager(s) (PAMs) and would be linked to post-market evidence generation and factors that contribute to an antibiotic's value. Payments could adjust over time depending on measured value, potentially through evaluation of product availability, utilization, appropriate stewardship, effectiveness, or improvements in cost or quality.²⁰ Such a population-based payment model might be most impactful in the United States if implemented through Medicare, which covers a population at increased risk of resistant infections. And because private payers frequently develop reimbursement mechanisms that mirror Medicare's, a Medicare-based model might encourage private payers to pilot their own population-based payment models for antibiotics.

While different countries might test different models, international alignment around antibiotic development, access, and stewardship is another incentive option. The US government might consider collaboration with other nations to pool resources and engage in shared decisions. Multilateral contracting has the potential to provide a significant incentive to developers without financially straining individual payers. As a result, parallel investments and purchasing agreements among multiple nations could constitute a similar incentive as a MER. Parallel investments can encourage new antibiotic development, accommodate diverse regional priorities, and sustain more iterative financing. Eligibility criteria based on the WHO priority pathogens list or CDC threats report can guide participation in multilateral contracting by

aligning investments from multiple large purchasers, increasing their buying power, and providing developers more predictable returns in exchange for high-priority antibiotics.

Barriers and Circumstances Limiting Incentives for Antibiotics

Each of the incentives discussed face barriers that limit their implementation or impact. Some barriers are straightforward and easily understood, like the detrimental link between antibiotic revenue and volume sales, while barriers related to financial and political circumstances are complex and multidimensional. Stakeholders will need to develop creative solutions and compromise on some aspects to enable effective incentive policies.

A number of incentives are limited by their reliance on volume sales. While CMS's recent updates to the NTAP program and Congress's proposed DISARM legislation increase reimbursement for new antibiotics, the potential increases in sales are limited to the number of infections that occur. Because resistant infections can occur infrequently, these changes may not significantly impact revenues.

Similarly, the magnitude of reimbursement or reward will influence the type of companies that re-enter the antibiotic market. While some incentives are attractive to small and mid-sized developers, they may not entice larger developers back to the market. These include incentives like CMS's NTAP program, BARDA's Project BioShield funded post-market contracts, MERs less than \$1 billion, and population-based payments with limited payer engagement. Lower-worth incentives are unlikely to provide enough value for large developers to shift resources away from more profitable product development. And while incentives like MERs and population-based payments can reach a larger magnitude of revenue, pooling financing for large MERs or achieving widespread participation in population-based payment models requires lengthy negotiations and consensus-building.

Furthermore, convincing stakeholders to authorize awards at the needed magnitude may be difficult when there is limited evidence upon approval and a lack of robust methods to measure antibiotic value. Funders need to understand the potential value of new antibiotics in order to determine the appropriate and politically-feasible magnitudes of financial support for BARDA-based contracts, MERs, and population-based payment models. Accordingly, efforts to align stakeholders around updated methods to determine antibiotic value are ongoing (a more detailed discussion will follow in next section).

A lack of stakeholder consensus regarding eligibility criteria that might qualify antibiotics for different incentives is also a barrier to implementation. Perspectives differ on areas of unmet need and types of innovation that would be most beneficial to public health, and these differences can impede implementation of some medium- and longer-term incentives.

Consensus building extends timelines and may not guarantee universally accepted incentive designs. However, stakeholders acknowledge that incentives designed to bolster biodefense and address threats to homeland security remain valuable. Incentives tailored toward biodefense can provide additional developmental, manufacturing, or commercial capacities that may subsequently benefit a wider range of antibiotic development. Likewise, incentives designed to generate novel antibiotics according to the needs of one country may eventually benefit the wider global community.

Finally, administrative and financial complexity may limit the expediency and feasibility of implementing incentives like population-based payments and multilateral contracts. Multiple perspectives must shift toward updated ideas about what to pay for and how. Numerous stakeholders are necessarily involved in both establishing a shared understanding of antibiotic value and determining which potential antibiotics and system capacities are most desired. However, stakeholders are already engaged in the collaboration and consensus-finding that will underpin these longer-term efforts. Next steps toward a reinvigorated market for antibiotics will require sustained public and private action, guided by increasingly aligned priorities and incentives.

Overcoming Limitations through Improved Resources for Evaluation

Valuing Antibiotics

Better defining the value that an effective antibiotic provides to society will address some of the challenges associated with robust antibiotic investment. Antibiotics are valuable life-saving medicines, but because many have been used for decades, inexpensive generics that treat most infections are used as a reference point. Defining and recognizing the components that compose antibiotic value can lead to increased revenues and encourage additional investment in antibiotics. Longer-term incentives like population-based payments and multinational parallel investments depend on thorough and transparent valuations of antibiotics. While stakeholders are increasingly interested in exploring the different components of antibiotic value, consensus is lacking regarding which contribute the most to antibiotic value and how to characterize them.

Antibiotics have several unique characteristics that make them valuable and that should drive increased investment. For instance, innovative antibiotics can offer new mechanisms of action that are less susceptible to resistance mechanisms, improved safety profiles, or the option for oral administration. These characteristics contribute to the “STEDI” elements of antibiotic value that accrue to individuals and populations^{24,26}:

- (1) Spectrum value, the availability of narrow-spectrum treatment options which may limit adverse impacts on the normal gut microbiome;

- (2) Transmission value, the avoidance of infection among individuals in populations adjacent to those infected, sparing morbidity as well as limiting opportunity for resistance development;
- (3) Enablement value, the enablement of procedures that would otherwise risk serious infection (like surgery);
- (4) Diversity value, an increase in the diversity of pharmacologic mechanisms to target and eliminate bacteria, impeding the emergence of resistance among pathogens; and
- (5) Insurance value, the availability of antibiotics effective against potential infectious disease outbreaks and the rapid emergence of widespread resistance to alternate classes of antibiotics.

It remains challenging to determine the best criteria and methods to quantify the benefits of antibiotic treatment to individuals and populations. The significant component of antibiotic value arising from some of the positive externalities listed above has recently been detailed in several studies.²⁴ However, these studies are relatively new and stakeholders continue to debate their validity. In Europe, HTA is common and stakeholders are accustomed to modeling the value of medical products in quantitative terms. In the United States, however, these quantitative evaluations are not as widespread. **A common understanding of antibiotic value among both domestic and international policymakers can drive political action toward a pipeline of antibiotics to address the threat of AMR.**

In addition, increasing AMR awareness among patients, providers, and payers, and the role effective antibiotics play in its context, might result in a higher valuation of antibiotics by the public. Accordingly, the Wellcome Trust recently released a report to improve communications about AMR, underscoring the need to focus messaging on the threat AMR poses to modern medicine, that AMR affects everyone, and the case for immediate action.²⁷ Recent studies showing that secondary bacterial infections may be linked to severe COVID-19 cases and fatalities lend support to this message.²⁸ Thoughtful communications that elevate the public's understanding of AMR have the potential to encourage next steps among policymakers and healthcare stakeholders. Importantly, a better technical understanding of antibiotic value is fundamental to addressing the limitations that impact existing and proposed incentives for future antibiotics.

Utilization and Outcomes Data

Post-market data collection contributes to the understanding of antibiotic value, but can also provide practical information about patient outcomes and population health after treatment with novel antibiotics. Pre-market data characterizes the safety and efficacy of new antibiotics, but evidence of antibiotic effectiveness remains limited because approvals are based on non-

inferiority trials for a single indication. Improved post-market data collection can address some of these limitations and yield benefits that accrue to multiple stakeholders. For example, post-market data can enable developer-led label expansions, expand payer-led coverage decisions, and improve provider-led clinical guidance documents. Additional data generation can also lead to higher quality care and enable incentive options like population-based payment models.

When making coverage and reimbursement decisions, payers rely on existing evidence, which may be limited for new antibiotics. In time, additional post-market data might offer evidence that encourages payers to expand novel antibiotic coverage and reimbursement, and it might provide developers an opportunity to expand the use of their products or differentiate their antibiotic from others. This additional information can improve patient access to novel antibiotics, reduce intense medical care, and increase revenue for developers.

Health care providers are similarly influenced by the initially limited evidence of novel antibiotic effectiveness. At first, providers may be limited to prescribing novel antibiotics based only on FDA-approved indications. When difficult infections cannot be addressed by existing antibiotic options, providers may prescribe novel antibiotics off-label according to any additional evidence of effectiveness that may have emerged (for example, through case studies). However, increasing data collection that characterizes both on- and off-label prescribing might generate the evidence to allow providers and professional organizations to more rapidly update interim guidances and eventually issue new formal treatment guidelines.

Each of these stakeholders benefits from organized data characterizing antibiotic utilization and outcomes, information that is typically siloed among diverse hospitals and provider systems, and which may lack accompanying diagnostic information. Stakeholders must commit to supporting and improving data collection capabilities throughout the antibiotic product lifecycle, and incentives can bolster these efforts.

The Centers for Disease Control and Prevention (CDC) has efforts underway to support post-market data collection and antibiotic stewardship in its National Healthcare Safety Network (NHSN). The NHSN's antibiotic use (AU) and antimicrobial resistance (AR) options offer facilities new tools to determine benchmarks, promote stewardship, and help track resistant infections.²⁹ While these antibiotic-specific options are widely employed, they are not mandatory and are not reported to CMS.³⁰ The data collected and analyzed are primarily for health care quality improvement among reporting facilities, but also enable assessments of resistance at the regional and national levels.²⁹ While NHSN data provide an aggregate snapshot of antibiotic use and AMR in the U.S., more information is needed.

More complete datasets on infections and antibiotic use provide an opportunity to structure better incentives for new antibiotics. **Key readouts are needed to supplement current**

CDC data collection, including which antibiotics are used, which infectious species are detected, their resistance profiles, and clinical outcomes following treatment.

Global stakeholders interested in designing incentives like BARDA-based contracts and multilateral contracting need to understand the burden of AMR, how pooled financial resources might be applied to specific challenges, and ultimately whether investments result in measurable outcomes. More granular data can facilitate updated treatment guidelines and antibiotic breakpoints, which would improve the feasibility of including value-based measures in population-based payment models. Accordingly, support for new antibiotic development and commercialization should incorporate resources for enhanced diagnostic tools, data collection, and data sharing, which can in turn enable improved antibiotic incentive designs. Infrastructure for many of these needed systems overlaps with that needed for COVID-19 surveillance, and the pandemic may offer an opportunity to leverage these new systems for AMR tracking.^{31,32}

Opportunities for Action

Coordinating Antibiotic Valuation

Aligning stakeholders around a coordinated approach to estimating the value antibiotics bring to society and public health can enable the implementation of substantial incentive approaches. The authorities conducting assessments of antibiotics vary among nations, and understanding how they operate can help determine what might change to improve the market for antibiotics. Frequently, the ministry of health is responsible for determining antibiotic coverage and reimbursement, but authorities such as social health insurers, a national health service, centralized national councils or agencies, or regional authorities may be responsible for antibiotic reimbursement and pricing decisions. These authorities typically consider antibiotics' therapeutic benefits, relative benefits, safety, cost-effectiveness, and the medical needs of a population along with potential budget impacts. And among European nations, a systematic health technology assessment (HTA) is frequently included and guides this process.³³ While some of these activities lend themselves to implementing incentives like BARDA-based contracts and population-based payment models, more formal methods to consider additional components of antibiotic value are desired.

Because several European nations already systematically apply HTA, **existing collaborations such as EUnetHTA might contribute to the development and adoption of a common framework for valuing antibiotics.** Designing and promoting such a framework represents an opportunity to align HTA bodies, governments, and payers around antibiotic value. An important next step is formalizing which additional elements of antibiotic value are most impactful and can be realistically measured or modeled, as well as which require subjective consideration.²² Accordingly, global stakeholders are attentive to the UK's work piloting

subscription-based payments for antibiotics. Future efforts to reframe the value antibiotics offer in the context of both routine healthcare and AMR will doubtless follow.

In the United States, metrics characterizing antibiotic value can build on existing quality measures. Inpatient quality measures of admission length and readmission rates can be parsed according to treatment for infections and antibiotic use. Outpatient and long-term care quality measures of community infection transmission and rates of resistant infections could similarly form the basis for metrics of antibiotic value in the U.S. context. While some health system capacity exists to operationalize these metrics, linking aggregate and individual patient outcomes to specific antibiotic use remains challenging.

Establishing Enhanced Data Capture & Sharing

Collaborations to improve antibiotic use and outcomes data collection can be established among funders, developers, and providers. Improved data collection supports both the measurement of antibiotic value, guides clinical care decisions, and influences future investing in antibiotic development and commercialization. As previously discussed, improved data collection can enable and sustain new antibiotic incentives. While the CDC's NHSN provides a foundation for enhancing widespread data collection and sharing, CDC alone cannot compel hospitals and providers to allocate additional resources to tracking patient outcomes. **BARDA can consider including broader data requirements in future contracts with developers in exchange for financing post-market evidence generation. CMS can consider new incentives or penalties that relate reimbursement to enhanced data collection and sharing.**

Allocating Resources for Investment & Commercialization

Enhancing collaborations between domestic stakeholders can bolster the impact of new incentives. While the CDC, FDA, BARDA, CARB-X and others each has a tailored mission, all are committed to addressing the threat of AMR. **The CDC's AMR threat classifications (urgent, serious, and concerning) and FDA's QIDP designation provide starting points for thinking about where to focus resources.** Furthermore, actions within the US can provide an example for the international community, and US leadership can encourage commitment to multinational collaborations. Already, the Global AMR R&D Hub is working to increase the visibility and alignment of existing resources and investments to address AMR.³⁴ Work coordinating resources both within the United States and around the world contributes toward the potential to implement multilateral incentives like MERs and parallel contracting.

New incentives must be coordinated among domestic and international stakeholders. For example, population-based payment models designed to benefit both an immediate population

and an international population are more likely to attract broad interest and engagement. Widespread implementation of population-based payment models can sustain novel antibiotic revenue and contribute to the visible progress that underlies investor confidence in the antibiotics space. **A CMS demonstration project to pilot a population-based payment model under Medicare, while restricted to US beneficiaries, can inform similar pilots among commercial payers and public payers in other countries.** Basing a CMS demonstration on concepts already adopted in the UK and Sweden, including an expanded evaluation of antibiotic value and minimum guaranteed revenue for developers, can encourage consensus principals among diverse stakeholders. And the demonstration's associated design of value measures, enhanced data collection practices, and transparent payment process would contribute toward enabling the entire spectrum of antibiotic incentives.

To further facilitate data capture and potential population-based payment models, CDC and CMS can collaborate to design value measures that relate to unmet medical need. Because CDC is engaged in tracking and measuring the burden of AMR and can expand and accelerate their effort, CDC can help identify which infections represent the greatest threat. In parallel, CMS has the capacity to require additional data collection regarding patient encounters and outcomes. **Together, the two agencies can identify which infections are prevalent, increasing, and driving unmet medical need.** With this knowledge, measures characterizing patient outcomes and medical costs can be designed to support post-market evidence generation, in turn enabling new incentive mechanisms including expanded post-market contracting and population-based payment models.

BARDA can continue engaging in post-market contracting that supports critical early revenue for developers, sustains antibiotic availability, and contributes to continued evidence development. **The best contract designs will lower upfront commercialization costs and enable commercial efficiencies that encourage developers to develop and market antibiotics with multiple indications, or pursue developmental programs that include multiple antibiotics.** BARDA's recent agreement with Paratek Pharmaceuticals establishes a model for future contracts that signal the agency's commitment to developers' early commercial success and encouraging private investor confidence in antibiotics.

Conclusion

Improving the antibiotic ecosystem requires a series of incentives that bring about incremental change and collectively create a sustainable market for antibiotic products. To provide immediate effect, short-term mechanisms, like increased antibiotic reimbursements through CMS's NTAP program and effective antibiotic stewardship programs, are needed. Needed in the medium-term are mechanisms to more adequately support novel antibiotics during early commercialization, like the proposed DISARM legislation and BARDA's post-market

contracting mechanism. In the long-term, incentive mechanisms like population-based payments and international multilateral contracting will be important.

Implementing this series of steps requires multiple stakeholders to commit to the following activities:

- (1) Designing methods to determine the value of antibiotics, as informed by the perspectives of developers, providers, and payers.
- (2) Collaborating to expand and improve data collection that can inform investments in novel antibiotics and antibiotic payment reform by measuring the burden of antimicrobial resistance, specific antibiotic utilization, and patient outcomes.
- (3) Aligning both domestically and internationally around common investment goals and post-market incentives that can increase the impact of limited financial resources and encourage renewed private investment in novel antibiotics.

Each of these activities involves multiple stakeholders in the antibiotics ecosystem. Experts on health technology assessment can devise and promote methods for valuing antibiotics. The CDC and CMS, working with private health systems and payers, can collect additional data about antibiotics and the patients they affect. Finally, facilitators like the Global AMR R&D Hub and the G20 can continue their work promoting international alignment and cooperation among potential collaborators. Securing these commitments and achieving these goals can reinvigorate research and development, support appropriate stewardship, and ensure access to critical, life-saving antibiotics.

References

1. Core Elements of Hospital Antibiotic Stewardship Programs. Centers for Disease Control and Prevention. Published February 7, 2020. Accessed May 1, 2020. <https://www.cdc.gov/antibiotic-use/core-elements/hospital.html>
2. Verma S. Securing Access to Life-Saving Antimicrobial Drugs for American Seniors. CMS Blog. Published August 6, 2019. Accessed April 30, 2020. <https://www.cms.gov/blog/securing-access-life-saving-antimicrobial-drugs-american-seniors>
3. Exploring Opportunities to Reform Antimicrobial Payment and Post-Market Incentives. Margolis Center for Health Policy. Published January 2020. Accessed April 30, 2020. <https://healthpolicy.duke.edu/events/exploring-opportunities-reform-antimicrobial-payment-and-post-market-incentives>
4. Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospitals. Federal Register. Published August 16, 2019. Accessed May 1, 2020. <https://www.federalregister.gov/documents/2019/08/16/2019-16762/medicare-program-hospital-inpatient-prospective-payment-systems-for-acute-care-hospitals-and-the>
5. New Medical Services and New Technologies. U.S. Centers for Medicare & Medicaid. Accessed May 1, 2020. <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/newtech>
6. Fiscal Year (FY) 2021 Medicare Hospital Inpatient Prospective Payment System (IPPS) and Long Term Acute Care Hospital (LTCH) Proposed Rule (CMS-1735-P). CMS.gov. Published May 11, 2020. Accessed May 29, 2020. <https://www.cms.gov/newsroom/fact-sheets/fiscal-year-fy-2021-medicare-hospital-inpatient-prospective-payment-system-ipps-and-long-term-acute>
7. Roskam PJ. *Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act of 2015*; 2015. Accessed April 29, 2020. <https://www.congress.gov/114/bills/hr512/BILLS-114hr512ih.pdf>
8. McConnell M. *Coronavirus Aid, Relief, and Economic Security Act*; 2020. Accessed April 29, 2020. <https://www.congress.gov/116/bills/s3548/BILLS-116s3548is.pdf>
9. Courtney J. *Coronavirus Aid, Relief, and Economic Security Act*; 2020. Accessed April 29, 2020. <https://www.congress.gov/116/bills/hr748/BILLS-116hr748enr.pdf>
10. *Coronavirus Aid, Relief, and Economic Security Act*; 2020. Accessed April 29, 2020. <https://www.congress.gov/114/plaws/publ136/PLAW-114publ136.pdf>
11. *Food and Drug Administration Safety and Innovation Act*; 2012. Accessed April 29, 2020. <https://www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf>

12. *Qualified Infectious Disease Product Designation Questions and Answers Guidance for Industry*. Food and Drug Administration; 2018. Accessed April 29, 2020. <https://www.fda.gov/media/111091/download>
13. Paratek Awarded BARDA Project BioShield Contract for NUZYRA®. Paratek Pharmaceuticals, Inc. Published December 18, 2019. Accessed April 29, 2020. <https://investor.paratekpharma.com/news-releases/news-release-details/paratek-awarded-barda-project-bioshield-contract-nuzyrar>
14. ASPR Blog Series: Combatting Antibiotic Resistance - PHE. Accessed November 29, 2016. <http://www.phe.gov/about/barda/Pages/antibiotic-resistance.aspx>
15. BARDA's Rapidly Expanding COVID-19 Medical Countermeasure Portfolio. Accessed May 29, 2020. <https://www.medicalcountermeasures.gov/app/barda/coronavirus/COVID19.aspx>
16. O'Neill. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. dReview on Antimicrobial Resistance; 2016. Accessed November 2, 2016. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
17. Ardal C, Findlay D, Savic M, et al. *Revitalizing the Antibiotic Pipeline: Stimulating Innovation While Driving Sustainable Use and Global Access*. DRIVE-AB; 2018. Accessed April 29, 2020. Stimulating innovation while driving sustainable use and global access
18. Chatham House Working Group on New Antibiotic Business Models. *Towards a New Global Business Model for Antibiotics*. Chatham House Accessed November 30, 2016. https://www.chathamhouse.org/sites/files/chathamhouse/field/field_document/20151009NewBusinessModelAntibioticsCliftGopinathanMorelOuttersenRottingenSo.pdf
19. Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's efforts to foster discovery and development of new tools to fight antimicrobial-resistant infections. U.S. Food and Drug Administration. Published June 16, 2018. Accessed April 29, 2020. <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-efforts-foster-discovery-and-development-new-tools>
20. Schneider M, Daniel GW, Harrison NR, McClellan MB. *Delinking US Antibiotic Payments through a Subscription Model in Medicare*.; 2020:13. https://healthpolicy.duke.edu/sites/default/files/atoms/files/margolis_subscription_model_14jan2020.pdf
21. Daniel GW, McClellan MB, Schneider M, Qian J, Lavezzari G, de Graffenreid E. *Value-Based Strategies for Encouraging New Development of Antimicrobial Drugs*. Duke-Margolis Center for Health Policy; 2017. https://healthpolicy.duke.edu/sites/default/files/atoms/files/value-based_strategies_for_encouraging_new_development_of_antimicrobial_drugs.pdf
22. Karlsberg Schaffer S, West P, Towse A, et al. *Assessing the Value of New Antibiotics: Additional Elements of Value for Health Technology Assessment Decisions*. The Office of Health Economics; 2017. <https://www.ohe.org/system/files/private/publications/OHE%20AIM%20Assessing%20The%20Value%20of%20New%20Antibiotics%20May%202017.pdf>
23. *Developing and Testing Innovative Models for The Evaluation and Purchase of Antimicrobials (Activity 1: Evaluation Framework)*. National Institute for Health and Care Excellence

24. Rothery C, Woods B, Schmitt L, Claxton K, Palmer S, Sculpher M. *Framework for Value Assessment of New Antimicrobials: Implications of Alternative Funding Arrangements for NICE Appraisal.*; :178. <http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf>
25. *Proposal – Economic Model for New Antibiotics.* Läkemedelsindustriföreningens Service AB (LIF); 2016. https://www.lif.se/contentassets/fa41395ff37d47a8acf5ca7da7a027e0/20160829-proposal_new_economic_model-antibiotics_eng_final.pdf
26. Outterson K, Rex JH. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Transl Res.* Published online February 20, 2020. doi:10.1016/j.trsl.2020.02.006
27. *Reframing Resistance: How to Communicate about Antimicrobial Resistance Effectively.* Wellcome Trust; 2019. <https://wellcome.ac.uk/sites/default/files/reframing-resistance-report.pdf>
28. Cox MJ, Loman N, Bogaert D, O’Grady J. Co-infections: potentially lethal and unexplored in COVID-19. *Lancet Microbe.* 2020;1(1):e11. doi:10.1016/S2666-5247(20)30009-4
29. National Healthcare Safety Network (NHSN) Patient Safety Component Manual: Antimicrobial Use and Resistance (AUR) Module. Published online January 2020. Accessed April 30, 2020. <https://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf>
30. FAQs: Antimicrobial Resistance (AR) Option | NHSN | CDC. National Healthcare Safety Network (NHSN). Published February 10, 2020. Accessed April 30, 2020. <https://www.cdc.gov/nhsn/faqs/faq-ar.html>
31. McClellan M, Gottlieb S, Mostashari F, Rivers C, Silvis L. *A National COVID-19 Surveillance System: Achieving Containment.* Duke-Margolis Center for Health Policy; 2020. https://healthpolicy.duke.edu/sites/default/files/atoms/files/a_national_covid_surveillance_system_withcover.pdf
32. Mostashari F, McClellan M. *Data Interoperability and Exchange to Support COVID-19 Containment.* Duke-Margolis Center for Health Policy; 2020. https://healthpolicy.duke.edu/sites/default/files/atoms/files/data_interoperability_and_exchange_to_support_covid-19_containment_final.pdf
33. *2015 Global Survey on Health Technology Assessment by National Authorities: Main Findings.* World Health Organization; 2015.
34. Objectives – Global AMR R&D Hub. Published 2019. Accessed April 30, 2020. <https://globalamrhub.org/our-work/objectives/>