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Exploring Opportunities to Reform Antimicrobial Payment and Post-Market Incentives

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Discussion Guide

Introduction

The threatening consequences of antimicrobial resistance (AMR) are growing and global, and multifaceted strategies to combat it are necessary. While a golden era of antibiotic discovery during the late 20th century gave rise to many therapies still used today, resistance mechanisms and their dissemination have eroded the effectiveness of several treatments.[1] Since then, the pace of antibiotic research and development has slowed.[2] The prospect of limited return on investment (ROI) due to challenging discovery research, non-inferiority clinical trials, small patient populations, limited diagnostic capabilities, and highly uncertain commercial markets has limited developer interest in novel antibiotics.

This lack of economic sustainability is an important factor in the slow pace of antibiotic development and commercialization. Limited returns discourage developers from investing in robust antibiotic product pipelines. All the while, the critical need for diverse new antibiotics has elicited a variety of potential policy solutions—from enhanced funding and support for discovery research and preclinical development to the potential appeal of large post-approval market entry rewards. A wide array of stakeholders are engaged in work to sustain the global antibiotic marketplace. Regardless, revenue generation remains a major barrier to sustainability, and until mechanisms are implemented to address this gap, investment in antibiotics will remain scarce.

Consequences of Resistant Infections

Complicated bacterial infection can result in severe patient morbidity and costly healthcare. These negative consequences are especially prevalent when initial treatments fail, and providers must decide how to care for patients with AMR infections. In the United States (US) alone, more than 2.8 million people suffer from resistant infections every year and 35,000 die as a direct result.[3] While the rate of mortality has decreased between 2019 and 2013, resistant infections remain a costly burden and continue to drive significant morbidity. Treating AMR infections has been estimated to add an additional $2.2 billion dollars to the annual cost of healthcare.[4] When antimicrobials fail, patients risk severe complications—colitis and toxic megacolon from *Clostridium difficile*, reproductive complications from *Neisseria gonorrhoeae*, paralysis from *Campylobacter*, reactive arthritis from *Shigella*, and others.[5] Even effective antibiotics put patients at risk of serious adverse events—especially patients with complicated resistant infections—who may experience allergic reactions, severe diarrhea, dehydration, or drug interactions that exacerbate routine side effects.[3] Despite intensive treatment, too many patients suffer devastating outcomes. Preventing treatment failures and serious adverse events requires clinicians to provide the right drug to the right patient at the right time. Unfortunately, the prevalence of infections lacking effective therapeutic options and the inappropriate use of antimicrobials complicates care. Without novel antimicrobials, existing options will likely become less effective as pathogenic organisms continue to evolve and acquire resistance mechanisms.

A Challenging Market for Antibiotics

While novel antibiotics are desired, generating return on investment (ROI) has become especially challenging for innovators. From the outset, clinical development is costly, and even more so for indications like resistant infections where patient populations may be limited. Further, most antibiotics are approved based on non-inferiority trials that do not demonstrate whether an investigational antibiotic is superior to the standard of care. This trial design means that new antibiotics enter the market with evidence demonstrating effectiveness that is at best equivalent than the current standard of care. In contrast, most other therapeutics have evidence demonstrating superiority to standard of care. This lack of data both slows the adoption of novel antibiotics over less expensive generics and discourages reimbursement commensurate with innovation addressing AMR.

Even when a new antibiotics is supported by evidence and approved for reimbursement, its utilization remains restricted by stewardship protocols, which guide physicians toward appropriate prescribing that aims to prevent potential resistance. While restricting inappropriate antibiotic use is important to maintain product effectiveness, stewardship practices restrict utilization and limit the revenue new antibiotics—even those with innovative mechanisms of action—receive under fee-for-service (FFS) payment schemes. As a result, developers are leaving the space and investing in more profitable product pipelines, as demonstrated by several recent departures.[6,7] Strategies are needed to encourage innovators to continue investing in antimicrobial research and development.

Prior Duke-Margolis Work on AMR

To facilitate progress toward a reinvigorated market for antimicrobials, over the past year and a half, and with support from the Wellcome Trust, the Duke-Margolis Center for Health Policy has convened experts from across the AMR landscape to address the potential implementation of domestic policy approaches and the global coordination of promising market incentives. The Margolis Center has advanced these 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 pull incentives; and (3) supporting the development of principles and approaches for global coordination. From these convening activities, as well as from discussion at the January 16th meeting, Duke-Margolis will publish a report of recommended actions and potential next steps. For a detailed overview regarding a potential subscription-based payment model, see the recent Margolis Center brief—*Delinking US Antibiotic Payments through a Subscription Model in Medicare*.

The purpose of the Margolis Center's public meeting is to highlight activities that have been executed over the past year and identify potential promising strategies and actions to improve the antimicrobial development ecosystem. Sessions will cover promising payment reform models, as well as other areas of the healthcare system that could be leveraged to improve antimicrobial utilization and evidence generation on outcomes and value. To provide background, this discussion guide will outline the underlying challenges of antibiotic development, highlight recent actions, and describe areas for future progress.

Pre- and Post-Market Development Incentives

As described above, the market for antibiotics is generally regarded as providing insufficient or even non-existent return on investment.[8] Relative to the public health value effective antibiotics offer, this limited return underscores the gap between financial support for pre-market antibiotic development and post-market commercialization. Regardless, opportunities to address challenging finances exist throughout the entire antibiotic product lifecycle, from pre-clinical and clinical development to post-market return on investment. As a result, stakeholders in the public and private sectors increasingly support a continuum of both push (pre-product approval) and pull (post-product approval) incentives.

Push Incentives for Antibiotics

Push incentives are intended to encourage antibiotic development by removing financial barriers or providing funding during pre-clinical and clinical research. Several well-established initiatives provide financial support for research and development efforts addressing AMR (Table 1). Together, this network of initiatives and global funders have implemented various push incentives designed to foster novel therapeutics, diagnostics, devices, and preventatives, as well as efforts to support the surveillance, stewardship, and the optimization of existing antibiotics. In the US, CARB-X announced it has funded 54 projects with investments totaling $179.3 million, and BARDA signaled its intention to explore a new bilateral venture capital partnership in support of antimicrobial innovation.[9,10]

Table 1: Major Push Incentive Funders[11]

Organization[a]	Budget	Development Stages Supported
BARDA[†]	$660M (FY2015 – 18)[12-14]	Phase 1 to regulatory approval
CARB-X	$550M (2016 – 21)[15]	Hit-to-lead to end of Phase 1
GAMRIF[†]	£50M (2013 – 21)[16]	Discovery research to end of Phase 1
GARDP	€270M (2017 – 23)[17]	All stages & patient access
Global AMR R&D Hub	€500M (2018 – 2028)[18]	AMR research coordinator (initial focus)
IMI ND4BB	€650M (2014 – 20)[19]	Entire value chain
JPIAMR	€234M (2012 – 24)	Discovery research
NIH[†]	$2,002M (FY2014 – 18)[20]	Discovery research to Phase 2
REPAIR Impact Fund	$165M (2018 – 23)	Lead optimization to end of Phase 1
Wellcome Trust[†]	$155M (2016 – 21)[21]	Policy & hit-to-lead to end of Phase 1

[†] NIH, BARDA, GAMRIF, and Wellcome Trust each contribute to the $550M CARB-X budget. NIH and BARDA direct $10M and $55M, respectively, toward CARB-X annually. GAMRIF is directing £20M toward CARB-X over three years.[22] Wellcome Trust is directing $155M toward CARB-X over five years.

[a] BARDA – Biomedical Advanced Research and Development Authority; CARB-X – Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator; GAMRIF – Global AMR Innovation Fund; GARDP – Global Antibiotic Research & Development Partnership; IMI ND4BB – IMI programme New Drugs 4 Bad Bugs; JPIAMR – Joint Programming Initiative on Antimicrobial Resistance; NIH – National Institutes of Health; REPAIR – Replenishing and Enabling the Pipeline for Anti-Infective Resistance Impact Fund

In addition to incentives for research and development, efforts to improve the regulatory pathway for antimicrobials have had some success. In 2012, the Generating Antibiotic Incentives Now (GAIN) provisions became Title VIII of the Food and Drug Administration Safety and Innovation Act (FDASIA) and created FDA's qualified infectious disease product (QIDP) designation.[30] QIDPs are eligible for both Fast Track and priority review designations, and if approved, five years of additional marketing exclusivity. The GAIN provisions also committed FDA to updating guidance regarding the clinical development of antibacterial and antifungal drugs and development in areas of unmet need. In 2016, the 21st Century Cures Act established the limited population pathway for antibacterial and antifungal drugs (LPAD pathway).[31] For developers pursuing drugs intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs, the LPAD pathway allows FDA to approach its benefit-risk assessment with additional flexibility. FDA must consider the severity, rarity, or prevalence of the infection a drug is intended to treat and may approve products that would not have a favorable benefit-risk profile in broader populations.

Challenges Beyond Early Development Costs & Regulatory Streamlining

Although regulatory changes have provided some benefit, and push incentives have effectively financed early-stage antimicrobial development, distinct market challenges discourage later-stage product development, registration, and commercialization. Non-inferiority trials—while appropriate for the registration of antibiotics—provide limited evidence of comparative effectiveness, slowing the uptake of new products. This evidentiary gap limits pricing that might adequately sustain continued innovation and ongoing sponsor-initiated evidence development. Furthermore, even if new antibiotics are eventually determined to be safer or more effective than generic alternatives, widespread use depends on the availability of evidence regarding effectiveness and susceptibility to resistance. These conditions create upfront commercialization costs that most small and medium-size developers cannot afford when novel antibiotics reimbursement is limited.

In addition to substantial commercialization costs, practice guidelines and clinical protocols represent an additional hurdle for novel antibiotic products. Widespread antibiotic stewardship programs—while designed to slow AMR—limit the unit-sales that generate antibiotic revenue under FFS payment systems. Finally, rising reimbursement pressures and constrained hospital budgets prioritize the least expensive therapeutic options for individual patients, notwithstanding potential downstream or broader population benefits of effective AMR management. These persistent challenges underscore why further policy initiatives are needed to provide adequate financial support during later-stage development and following the approval of a potentially valuable new antibiotic.

Pull Incentives for Antibiotics

Even when push incentives help to offset pre-market costs, manufacturers still incur expenses to maintain their products, and within the current market, revenue generated by new antibiotic products do not cover these operational costs.[23-25] Pull incentives encourage development of antibiotics by providing a financial reward following the approval of a product, and often provide a mechanism to

supplement or supplant revenue generation. Pull incentives vary in form, and for this discussion, pull incentives will separated into two categories: reward models and payment reform.

Several pull mechanisms have been proposed to encourage antibiotic development, including the advanced market commitment (AMC), priority review voucher (PRV), transferrable exclusivity voucher (TEV), and market entry reward (MER).[8] AMCs have been successfully implemented for vaccines, but would need to be constructed so that they do not depend on unit sales. Several payment reform approaches apply this concept. Among the other reward models, TEVs and MERs are viewed as more attractive mechanisms for antimicrobials, whereas PRVs may not generate sufficient revenue for antimicrobial developers. TEVs extend the market exclusivity of an existing biopharmaceutical product, and are attractive because they would likely generate substantial revenue through additional product sales or sale of the voucher.[8] A TEV has the potential to drive value for both large and small developers and maintains budget neutrality. However, sustaining the higher prices of existing drugs raises concerns about the affordability of current high-cost treatments, and legislative proposals to implement TEVs may not be politically feasible.

A MER avoids some of the challenges facing other pull incentives. According to a thorough literature review and stakeholder analysis conducted by DRIVE-AB, an entry reward is the most commonly recommended potential pull incentive.[2] Such a reward would likely take the form of multiple annual payments to a developer following the approval of a new antimicrobial. To ensure the availability and stewardship of a new antimicrobial, payments would be contingent upon contractual conditions between the payer and developer. These payments could occur in equal installments, differential installments, or installments adjusted according to unit-sales to ensure consistent revenue for the developer. There is considerable policy interest in understanding how MERs can be designed and implemented.

Successfully implementing and sustaining a large pull incentive such as a MER will require a new type of financial commitment, and policymakers will need to address various financing considerations, eligibility criteria, and contractual conditions. The size and scope of an entry reward will guide its intended impact and influence which stakeholders may be incentivized to invest in antimicrobials as a result. Entry rewards could be structured to sustain investments among small-to-medium developers and their financiers, or to additionally encourage the market re-entry of large multinational developers. MERs could also function to differentially incent the development of novel antimicrobials with desirable features, like activity against hard-to-treat gram-negative infections or immunity from defined resistance mechanisms. By multiple estimates, MERs designed to attract larger multinational developers will need to offer around $1 billion worldwide, excluding revenues.[8] Such a figure is likely to require substantial public financing and thereby obligates governments to ensure their investments are likely to return significant population health value. Thus, in addition to deciding which microbial threats are most severe and which novel antibiotics may be eligible for a MER, stakeholders must also consider how existing payment reforms could support antibiotic availability.

Payment Reform Approaches to Support the Antibiotic Market

Payment reform approaches are another option for providing a pull incentive for antibiotics by improving the market for new products. Payment reform approaches may not deliver the same magnitude of return as a reward model incentives, but may present a more practical and sustainable

path to market correction, with the added benefit of incentivizing value-based care at the population level. While there is no straightforward solution to address the complex challenges created by AMR and antibiotic development, collectively, stakeholders have been making progress that serves as a foundation for future action. New incentive approaches will have varying levels of feasibility, and the trajectory of each mechanism will contribute to a more sustainable path for addressing AMR.

Near-Term Payment Reform Approaches

Under Medicare Part A and its Inpatient Prospective Payment System (IPPS), inpatient-administered drugs are accounted alongside related hospital services, collectively assigned a diagnosis-related group (DRG), and reimbursed as a bundled global payment. New expensive drugs that add to the cost of treating infections covered by defined DRGs will reduce net revenues for providers. As a result, hospitals may seek to limit the utilization of expensive drugs, impacting patient access to innovative therapeutics.

To promote product uptake and reduce the financial burden on hospitals using innovative but expensive medical products, CMS introduced the New Technology Add-On Payment (NTAP) in 2000. The NTAP program provides additional reimbursement for new drugs or devices whose costs exceed the amount covered under the existing DRG, and that demonstrate substantial improvement over existing technologies. Developers must apply for their product to qualify, and approved NTAPs now cover up to 65% of the cost of the technology not covered by the DRG. A medical product may receive NTAPs for two to three years, but developers must apply for renewal each year. As the new technology is adopted among providers during this period, the applicable DRGs are intended to adjust by incorporating the cost of the new technology. However, for rarely used products, this adjustment may inadequately support ROI upon expiration of NTAP eligibility.

The final version of the CMS Fiscal Year (FY) 2020 IPPS rule reformed antibiotic reimbursement, taking steps to better support innovative products. The new rules from CMS are intended to neutralize the difference in costs to the hospital in the use of generic versus new antibiotics. CMS made two antibiotic-specific changes to the NTAP program and updated how resistant infections can be coded by hospitals. First, through the NTAP program, CMS will pay hospitals 75% of the costs not reimbursed by the DRG when a qualifying antibiotic is used. Second, CMS has waived one of three criterion for receipt of the NTAP for qualifying antibiotics: qualifying antibiotics no longer need to demonstrate substantial clinical improvement over existing treatments. Because antibiotics generally utilize non-inferiority trials for regulatory approval, substantial clinical improvement is particularly hard to demonstrate before a product reaches the market. And finally, CMS has changed the severity score for eighteen types of resistant infections, which will increase reimbursement through the IPPS, reflecting the increased costs associated with treating resistant infections.

Comments from Duke-Margolis and other stakeholder groups recommended additional steps that CMS could take to ensure that hospitals are reimbursed sufficiently to encourage the development and appropriate use of new antibiotic products. While these proposals are similar in purpose to the reforms described above, they would be more impactful in the view of various stakeholders, including manufacturers. Under Medicare, one option is removing the reimbursement of new antibiotics from the DRG-based IPPS. This would shift antimicrobial reimbursement to Part B, where providers are reimbursed according to the average sales price plus six percent. In commercial settings, the reimbursement amount would vary among payers. Such a carve-out mechanism would likely reimburse

hospitals based on an average of purchase price of qualified antimicrobials, mitigating financial considerations impacting hospital pharmacy procurement and the treatment options available for patients. Like an enhanced NTAP, such a measure would increase reimbursement for innovative antibiotics and speed their inclusion on hospital formularies. An example of proposed legislation to address this need is the DISARM bill, which was recently introduced in the Senate (S.1712).

De-Linking Antibiotic Product Revenue from Sales Volume

While changing the payment mechanism or amount of reimbursement could bolster novel antimicrobial revenue in the short-term, this approach nonetheless depends on the volume of product sold. Infrequently used antimicrobials (such as those new to the market) may not benefit significantly from such approaches. A transition to approaches that delink the payment for antibiotics from the volume of their use could prove more sustainable in the long-term, achieving some of the goals of a MER while working through insurance payments that, in the US and elsewhere around the world, are moving from volume- to value-based approaches.

Proposals from several global stakeholders have suggested implementing 'delinked' payment models, in which revenue for an antimicrobial is delinked from sales volume. Delinkage mechanisms shift from paying per dose used to paying for antibiotic availability. Purchasing antibiotics on a subscription basis is one approach to delinking revenue and volume. A subscription model could provide access to the antibiotic for a flat and predictable recurring payment, potentially linked to antibiotic performance goals. Paying for the availability rather than use of a qualifying antibiotic could enable several benefits.

First, such models would guarantee revenue streams for those developing effective priority antibiotics, regardless sales volumes. Second, these models could eliminate the need for developers to drive increased product uptake, aligning payment with appropriate prescribing and stewardship goals. Third, these models could potentially enable payments to reflect the additional components of population health value provided by effective antibiotic treatment. Measuring these value components could support the collection of data on an antimicrobials' real-world effectiveness, including whether resistance rates in covered populations subsequently decrease.

International Payment Reform Pilots

Other countries are beginning to explore implementation of delinked payment models. In the United Kingdom (UK), the National Health Service and National Institute for Health and Care Excellence (NICE) will be testing a new type of payment model for antibiotic. The UK will be employing a subscription-like payment mechanism that will pay for antibiotics based on availability and value rather than the number of doses that are used. This concept reflects some of the ideas presented in the prior Duke-Margolis Priority Antibiotic Value and Entry Award, including linking payments for an antibiotic to its impact on AMR in a population.[26] The UK reimbursement mechanism will use new modeling parameters within their traditional health technology assessment (HTA) to encompass elements of population health value that are not normally considered. This model will initially be tested with a limited number of antibiotics, and actual reimbursement rates are yet to be determined. However, implementation will be closely watched, and if successful, stakeholders in other countries may consider adopting similar approaches.

In Sweden, the Public Health Agency has developed a pilot model that would guarantee a certain level of revenue from the government to an antimicrobial developer regardless of the volume of antimicrobial

used.[27] The purpose of this model is to encourage market entry and enable access to the new antimicrobial if needed. The pilot will include two antibiotics that have remaining market protections, are used in low volumes, and are of special medical value. The fee paid to the developer would be based on estimated volume needed. This model has yet to be implemented, so it is unclear if the total payment would effectively ensure access. However, it is feasible that if this model were implemented by multiple countries, then the accumulated premiums may provide a substantial return to the antimicrobial developer.

Value-Based Payment Models in the United States

Shifts across the US healthcare sector have been placing greater value on evidence-based treatment and quality outcomes. In particular, payers and manufacturers within and outside of the US have begun experimenting with valued-based payment (VBP) arrangements, where drug reimbursement is dependent in part on the delivered outcomes.

VBP models represent an additional opportunity to emphasize and reward the value that qualified antimicrobials contribute to high-quality healthcare, and typically take either of two forms: evidence-based pricing and outcomes-based contracts. When determining payment for a product, evidence- or indication-based pricing considers existing evidence, such as evidence generated in clinical trials. In contrast, outcomes-based contracts determine payment for a product based on evidence generated through real-world use. These types of payment contracts may incorporate rebates paid by developers to payers if pre-defined outcomes in individual patients or populations do not result from appropriate product use. Outcomes-based contracts also include population-based payments, where payments are contingent on population-level rather than patient-level outcomes. Population-based payments will likely depend on meaningful outcome measures and require greater provider involvement.

Few truly population-based contracts for drugs have been implemented, but stakeholders are beginning to pilot such arrangements. The state of Louisiana recently announced its intention to implement a subscription payment model for hepatitis C therapies. Under the arrangement, Louisiana's Medicaid program will pay a set fee to the drug developer for unlimited access to the therapy. Outcomes are not being tracked under this arrangement; evidence is already strong on the effectiveness of recent hepatitis C therapies, and so the model is primarily focused on achieving greater access without increasing program costs. However, given the significant number of patients who are undiagnosed and may have difficulty with screening and follow-up even with a low drug price, this kind of payment arrangement could include adjustments for population outcomes, including cure rate, adverse events, or reductions in the downstream costs of disease complications.

There are several reasons why antibiotics for resistant organisms may be appropriate for VBP arrangements. For one, when effective, antibiotics have the potential to lower costs by reducing health care utilization and averting additional infections. An important benefit of treating resistant infections accrues to the members of a population who are spared subsequent infection and treatment owing to the appropriate treatment of prior infections among the population. VBP arrangements based on population outcomes (e.g. prevention of subsequent resistant infection) or models where payments are completely delinked from sales volume may better align payment for antibiotics with the population health values they offer.

Another potential advantage of VBP arrangements for antibiotics that target resistant infections is the potential to improve stewardship and appropriate prescribing. Clinical trials often generate limited evidence regarding the real-world effectiveness of such antibiotics. Furthermore, new antibiotic approvals trend toward narrower patient populations and their effectiveness across broader and more diverse use cases may be uncertain. As providers and health systems generate additional data about the utilization of novel antibiotics, better determinations regarding how and when an antibiotic may be effectively employed can improve prescribing. Coordinating antibiotic utilization with enhanced and timely data collection can simultaneously support value-based arrangements and appropriate prescribing. Stewardship programs benefit from detailed utilization and outcome data and health systems can drive the efficiencies underpinning value-based arrangements where data is already being collected for stewardship purposes.

Developing Population-Based Payments for Antibiotics

As additional steps are considered to improve the link between the public health value that antibiotics offer and the amount that they are reimbursed, one option is a population-based approach, which could be used to delink payment from volume use. A subscription model is one form that this approach could take. In June 2018, the former Commissioner of Food and Drugs suggested a model in which CMS would pay a subscription or licensing fee for antimicrobials access, and where FDA and CMS would work in coordination to determine eligibility for this new pathway.[28] Payments to the developers would likely be contingent on certain milestones or outcomes being met, as well as continued availability of the drug.

Building on this suggestion, Duke-Margolis developed a framework for implementation in Medicare, where antibiotic payment would occur through a recurring fee that is linked to evidence generation and ongoing demonstration of value.[29] Using this approach, product manufacturers would work with CMS prior to approval to include endpoints or readouts relevant to the value of the antibiotic. Because this type of arrangement would be a fundamental change from the current volume-based purchasing approach, new structure will be needed for procurement and distribution to hospitals. Our framework suggestions that creation of Priority Antibiotic Manager(s) (PAMs), which would be responsible for the purchasing of antibiotics on a subscription basis, distributing antibiotics to the providers (potentially with a nominal fee per use), and collecting and processing data on antibiotic use and outcomes. These entities would be competitively-selected by CMS. To promote appropriate use of the new, priority antibiotics, CMS would continue to rely on its antibiotic stewardship requirements.

The subscription payment to the manufacturer would not be based on the sales volume of the antibiotic, but would assure that an adequate supply was available for Medicare beneficiaries. An advance payment made to the priority antibiotic manufacturer would provide some measure of predictable revenue, and this payment would take into consideration two components. One part would be based on expected need within the Medicare population when the drug, which would address concerns about hospital incentives to obtain and use the antibiotic appropriately. The second component would be reflect value beyond what is captured in actual use by beneficiaries. Some of these values, such as the potential for reduced transmission, expanded access to medical services, and drug novelty are further described in the next section. Over time, payments could be adjusted as additional evidence around value is generated.

Data collection and tracking of key measures will be critical to the success of this model. Valuable measures might focus on ensuring antibiotic availability when needed, tracking when and for what the antibiotic is used, and quantifying the overall cost of AMR through tracking care duration and intensity or presence of resistance. These data collection efforts could align with CDC and other public health organization efforts on stewardship and surveillance, representing an opportunity to better quantify the societal benefits of combatting AMR. Pairing data collection with payment reform efforts will directly align antibiotic payments with public health goals and with Medicare's shift from volume- to value-based payments for other important components of medical care.

Sustaining the Market for Antimicrobials through Improved Valuation and Evidence Development

Rigorously quantifying the value of novel antimicrobials stands to improve the prospect for their rapid coverage and increased reimbursement among payers. However, multiple factors comprise the value of an antimicrobial and consensus regarding which components can be formally defined remains elusive. Determining the criteria and methods to quantify the benefits of antimicrobial treatment that accrue to individuals, and moreover the populations to which they belong, remains challenging. The significant component of antimicrobial value arising from their positive externalities is the subject of relatively nascent study.

For instance, a study on surgery and cancer care demonstrated that surgical site infections and infections following chemotherapy are increasingly resistant to first line antimicrobials. In the absence of novel antimicrobials, and if effectiveness of current antimicrobials were to be reduced by 30%, an estimated 120,000 additional surgical site- or chemotherapy-associated infections would occur every year (in the US).[30] The availability of novel antimicrobials might mitigate predicted increases in treatment-related mortality, estimated to be between 2,000 – 15,000 deaths per year.[30,31] Effective antimicrobials have the potential to lower downstream health care costs by reducing health care utilization following complicated infections, as well as by preventing additional infections.

Beyond enabling procedures that would otherwise risk serious infection (like surgery), stakeholders have identified four additional elements of value that accrue at the population health level: (1) avoidance of infection in populations adjacent to infected individuals and slowing the development of resistance; (2) diversity of pharmacologic mechanisms to target bacteria, impeding the emergence of resistance among pathogens; (3) narrow-spectrum treatment options which might reduce adverse effects on the natural gut microbiome; and (4) "social insurance" against potential disease outbreaks and the rapid emergence of widespread resistance to alternate classes of antimicrobials, both within and beyond the US.[32] Preventing the development and spread of new infections is anticipated to be highly valuable to the health care system because of the potential costs associated with these infections, and from a patient perspective, lack of transmission means that there is reduced risk for adverse events and loss of productivity. Further development of methods to quantitatively and comprehensively value antimicrobials, and collecting evidence of their impact on individual and population health outcomes, would provide a stronger foundation for payment models for antibiotics that reflect these distinctive sources of value.

Expanding and Delivering on Antimicrobial Value

While the majority of infections are cured following first-line antimicrobial therapy, difficult-to-treat and resistant infections require more sophisticated interventions and system-level strategies. Rapid diagnostics, non-traditional antimicrobial treatments, antimicrobial stewardship programs, and enhanced local and global surveillance can each contribute to a future where resistant infections are easily identified and eliminated.

Rapid diagnostics are desired not only for their immediate impact on clinical practice, but for their effect on developers' interest in pursuing innovative narrow-spectrum antimicrobials. Unfortunately, as with novel antimicrobials, securing reimbursement for new diagnostics is often challenging or unclear, discouraging device makers from entering the market. However, incentivizing the development of diagnostics that enable rapid and appropriate prescribing can increase the value of antimicrobials. Diagnostics that enable providers to move beyond empiric prescribing stand to mitigate the adverse effects of inappropriate treatment, including potential toxicity, intensive or extended inpatient care, and the risk of facilitating the emergence of resistance (by exposing infectious organisms to antimicrobials which may be incompletely effective).

Another avenue toward enhancing the value of both novel and existing antimicrobials depends on the effective design and implementation of stewardship and surveillance programs. The CDC has developed and disseminated core elements of effective stewardship programs, and as of March 2020, hospitals participating in Medicare are required to implement stewardship programs.[33,34] However, further steps can be taken to advance stewardship and surveillance efforts. As was previously discussed, actionable data regarding the utilization of antimicrobials at the local level can inform how and when an antimicrobial may be most effectively employed, or when resistance might be anticipated. Collecting and analyzing reliable data following the utilization of antimicrobials is increasing in prevalence and scope. Provider systems with the resources to pursue these strategies—designing stewardship protocols to encourage appropriate prescribing and data infrastructure to detail use cases and patient outcomes—are encouraged to do so. As these practices expand and become more sophisticated, stakeholders will benefit from a more informed understanding of antimicrobial value.

Exploring Opportunities to Reform Antimicrobial Payment and Post-Market Incentives

The Margolis Center is committed to gathering the stakeholder community and working collectively toward a framework of near-term actions to mitigate AMR in 2020 and beyond. During the meeting, discussion will consider a wide range of policy priorities, including antimicrobial development and innovation, valuation and evidence development, payment reform, stewardship, and global coordination.

Session 1: Highlighting US actions on antimicrobial innovation, payment and stewardship

As the issue of AMR grows more urgent, government organizations have been using their authorities to take steps to address the problem. In this session. Speakers will provide an overview of domestic efforts to address the threat of AMR from the perspective of federal agencies, including the Centers for Disease Control and Prevention (CDC) and the Centers for Medicare & Medicaid Services (CMS). Discussion will focus on actions that have resulted in measurable impacts and challenges that remain to be addressed.

Session 2: Developing a path to improved and sustainable reimbursement for antibiotics

Limited return on investment has broken the antimicrobial market. While novel payment approaches may provide more predictable revenue, convincing developers, payers, and providers to pilot new mechanisms can benefit from more clearly defined antimicrobial value. Discussion will encompass the most likely path toward population-based payment models, and strategies to engage public- and private-sector stakeholders both domestically and across the globe.

Session 3: Exploring other actions that can contribute to a healthy antimicrobial ecosystem

Providers and payers are developing and implementing new technologies and improved information systems that can enhance the value proposition for utilizing novel antimicrobials. Ensuring the right patient receives the right therapy at the right time requires leveraging rapid diagnostics, ensuring appropriate stewardship, and collecting outcomes and to bolster post-market evidence. Participants will consider how current and future technologies and information systems can improve the adoption, utilization, and sustainability of novel antimicrobials.

Session 4: Next steps and reflections on the path forward

Progress toward a reinvigorated market for antimicrobials almost certainly depends on the implementation of thoughtful legislative and administrative incentives for investing in and sustaining innovative product pipelines. Policymakers are aware of the potential paths forward and will discuss near-term actions that build on the progress of the past year.

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