Duke | MARGOLIS CENTER *for* Health Policy

Economic Considerations for Implementation of an Antibiotic Pull Incentive

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Discussion Guide

Antimicrobial resistant infections pose a significant global threat and a robust arsenal of novel antibiotics is essential to ensure public health. Unfortunately, the prospect of low returns on investment (ROI), due to challenging discovery research, non-inferiority clinical trials, small patient populations, limited diagnostic capabilities, and highly uncertain commercial markets has ultimately led to poor market conditions and limited developer interest in novel antibiotics.

To address these challenges, a large pull incentive mechanism was proposed by the UK's Review on Antimicrobial Resistance and Europe's DRIVE-AB as a promising approach to encourage new antimicrobial development.[1,2] Yet generating and sustaining support for pull incentives has been difficult, even in areas where there is demonstrated public need.

There is still not consensus from key stakeholder groups about whether a large pull incentive is needed, and whether one can be designed and implemented in a way that would bring real value. To help maximize the impact of a pull incentive, the Duke-Margolis Center for Health Policy is convening this workshop to describe the value provided by antimicrobials, and explore the economic rationale for a pull incentive to address current market challenges and to ensure public health benefits. Discussion will also cover how a market entry reward might complement other incentives, how policymakers are likely to view potential proposals, and which potential funding mechanisms are most politically and administratively feasible.

Valuing Antibiotics

Antibiotics can increase life expectancy and improve quality of life. However, worldwide, approximately 700,000 deaths can be attributed to antimicrobial resistance (AMR), and the UK's Review on AMR has estimated that if resistance is left unchecked, that number could increase to 10 million deaths per year. In addition to high mortality, increased AMR could potentially cause significant economic losses throughout the world due to lost productivity and quality of life.[3] The Centers for Disease Control and Prevention (CDC) has also estimated that more than $20 billion in excess direct healthcare costs is attributable to resistant infections in the US.[4] Infections caused by high priority pathogens, like those identified by the CDC and World Health Organization (WHO) as urgent threats (Table 1), can result in tens of thousands of dollars in healthcare costs per patient (Table 2).

Table 1. CDC Pathogen Threats & WHO Priority Pathogens

CDC Pathogen Threats	WHO priority pathogens list for R&D of new antibiotics
Urgent Threats *Clostridium difficile* Carbapenem-resistant *Enterobacteriaceae* *Neisseria gonorrhoeae*	**Priority 1: CRITICAL** *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
Serious Threats Multidrug-resistant *Acinetobacter*	**Priority 2: HIGH** *Enertococcus faecium*, vancomycin-resistant

Drug-resistant *Campylobacter* Extended spectrum *Enterobacteriaceae* Vancomycin-resistant *Enterococcus* Multidrug-resistant *Pseudomonas aeruginosa* Drug-resistant non-Typhoidal Salmonella Drug-resistant Salmonella serotype Typhi Drug-resistant Shigella Methicillin-resistant *Staphylococcus aureus* (MRSA) Drug-resistant *Streptococcus pneumoniae* Drug-resistant Tuberculosis	*Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant *Heliobacter pylori*, clarithromycin-resistant *Campylobacter* spp., fluoroquinolone-resistant *Salmonellae*, fluoroquinolone-resistant *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant
Concerning Threats Vancomycin-resistant *Staphylococcus aureus* Erythromycin-resistant group A Streptococcus Clindamycin-resistant group B Strepococcus	**Priority 3: MEDIUM** *Streptococcus pneumonia*, penicillin-non-susceptible *Haemophilus influenzae*, ampicillin-resistant *Shigella* spp., fluoroquinolone-resistant

Table 2. Economic burden of select high priority bacterial pathogens identified by CDC and WHO

Pathogen	Healthcare costs per patient	Total costs per year	Infections per year[4]
Clostridium difficile	$13,168 - $28,218[5]	$4.8B[6]	500,000
CRE	$22,484 - $66 031[7]	$275M[7]	9,000
Methicillin-resistant *Staphylococcus aureus* (inpatient)	$14,000[8]	$478M - $2.2B[9]	368,600
Multidrug-resistant *Pseudomonas aeruginosa*	$99,672[10]	$667M[i]	6,700

Common hospital indications associated with high these priority pathogens, like complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), *C. difficile* infections (CDI), acute bacterial skin and skin structure infections (ABSSSI), and blood stream infection (BSI)/sepsis, result in significant healthcare spending for Medicare (Table 3). For example, *Clostridium difficile* infection (CDI) is an opportunistic infection, and frequently occurs because of prior broad spectrum antibiotic treatment. As a result, it is difficult to treat, and may recur in 20-30% of patients, with the rate of recurrence increasing to 40-60% after the first repeat event.[11] CDI impacts the elderly at a higher rate than the rest of the population, and it can be costly to treat: expenses are estimated to total $21,448 per patient, with an additional $15,050 spent for each recurrence.[12] The US is estimated to spend over $4 billion on CDI every year, so there are many opportunities for improved health and averted spending with this type of infection, whether preventing the first infection from occurring, or by preventing recurrent events.[6]

Table 3. Average costs of infection-associated indications in the Medicare population[ii]

Indication	Average Cost per Discharge	Number of discharges (2016)	Total Medicare spending (2016)

[i] Estimated based on Healthcare costs per patient and Infection per year

[ii] DRG codes used for analysis: cUTI (682, 683, 687, 689, 690), cIAI (371, 372, 373), CDI (193, 291, 292), ABSSSI (35, 602, 603), CABP (177, 178, 179, 193, 194, 195), BSI/sepsis (853, 870, 871, 872). Costs and discharges are averaged across total Medicare IPPS discharges in FY 2016 for each DRG code.

cUTI	$4,678 - $9,670	484,664	$60,767,621
cIAI	$4,537 - $11,474	35,614	$15,154,814
CDI	$5,956 - $9,415	552,276	$62,986,208
ABSSSI	$4,968 - $14,823	133,166	$21,671,793
CABP	$3,897 - $11,780	393,390	$75,498,995
BSI/sepsis	$6,325 - $40,041	802,739	$153,666,297

Resistant infections do not only have an impact on mortality; they also have indirect impacts on society in the form of lost productivity. The CDC has estimated that AMR results in over $35 billion in lost productivity per year.[13]

A range of diseases are associated with high and rising public health and economic burdens, yet have inspired limited investment to develop better treatments. However, some key features of AMR treatments imply that many of their potential benefits will not be considered and reflected in reimbursement decisions by health care providers and patients in the context of individual patient treatment decisions. These benefits are external to individual patients receiving treatment and include: 1) avoidance of infection in populations adjacent to infected individuals (i.e. indirect benefits to patients who do not receive treatment) ; 2) increase the diversity of mechanisms used to target bacteria, potentially slowing the development of resistance in future infected patients; 3) enable procedures that carry a high risk of infection, like surgery, in patients who would otherwise be at high risk of resistant infection; 4) enable narrow-spectrum targeting of pathogenic bacteria within individuals, to increase the ongoing availability of effective treatment; and 5) provide "social insurance" value against potential disease outbreaks and the emergence of rapid and widespread resistance to other antibiotics both within and outside the United States.[14] When effective, antibiotics for high priority infections have the potential to lower downstream health care costs through reduced subsequent health care utilization as well as averted additional infections. That is, major benefits of effective treatments for antimicrobial resistant bacteria accrue not to the individual instance of patient treatment, but to the members of a population who never need treatment because the treatment is available and used appropriately in a small number of patients to prevent spread of resistance.

AMR directly threatens the benefits of modern medicine for many patients, particularly those with underlying conditions that place them at greater risk of infection, as effective antibiotics are needed to enable common medical procedures like surgery, chemotherapy, or child birth. A study on surgery and cancer care demonstrated that surgical site infections and infections following chemotherapy are increasingly resistant to first line antibiotics. The availability of novel antibiotics might mitigate predicted increases in treatment-related mortality, which are estimated to be between 2,000 – 15,000 deaths per year.[15,16] In the absence of new antibiotics, and if effectiveness of current antibiotics were to be reduced by 30%, an estimated additional 120,000 surgical site- or chemotherapy-associated infections would occur every year in the US.[15]

Traditional "fee for service" (FFS) payment approaches are not well designed to provide adequate reimbursement for these features of antibiotics; rather, they reflect limited willingness to pay for the public health value of a robust antimicrobial treatment capacity beyond the patient at hand. "De-linkage" models have been proposed, which seek to pay more for availability of antibiotics that achieve

these public health benefits, such as through truly novel mechanisms of action, substantial narrow spectrum activity, and reduced toxicity.[17] However, these elements of value are often not reflected in reimbursement decisions for individual patients. In the European context, health technology assessment underpins the insurance coverage and reimbursement of most medical products and may require refinement in the antibiotic context. The Office of Health Economics and the Academy of Infection Management summarized multi-stakeholder discussions regarding the various elements of antibiotic value and how typical HTA assessments fail to consider the broader value of antibiotics.[18]

Clearly, discussions about policy reforms to modify incentives to develop antibiotics, and how these reforms can reasonably reflect present and future value that are not captured in current payment and other policies, are multifaceted and intertwined in financial, scientific, and political concerns. However, policymaker awareness of the appropriate methods for determining the social value of novel antibiotics is a critical foundation for determining how best to encourage additional development of these products in a way that increases public health benefits while avoiding unnecessary public and private costs.

Better Incentives for Antibiotic R&D: A Lifecycle Approach

The limited potential return on investment in antibiotic development relative to social benefits would imply a need for stronger financial support for antibiotic R&D and availability. Opportunities for such support 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 are increasingly focused on a continuum of both push and pull incentives.

Regarding push incentives, a number of organizations and initiatives have come together to provide financial support for development efforts that address AMR, including the Biomedical Advanced Research and Development Authority (BARDA), CARB-X (Combating Antibiotic Resistant Bacteria Accelerator), the Global AMR Innovation Fund (GAMRIF), the Global Antibiotic Research and Development Partnership (GARDP), the Global Antimicrobial Resistance Research and Development Hub (Global AMR R&D Hub), the Innovative Medicines Initiative (IMI) program New Drugs 4 Bad Bugs (ND4BB), the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), the National Institutes of Health (NIH), the REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund, and the Wellcome Trust (Table 4). Together, this network of global funders is implementing various push incentives designed to foster novel therapeutics, diagnostics, devices, and preventatives, as well as to support surveillance, stewardship, and the optimization of existing antibiotics.

Table 4: Major Push Incentive Funders[19]

Organization	Budget	Development Stages Supported
BARDA†	$660M (FY2015 – 18)[20–22]	Phase 1 to regulatory approval
CARB-X	$550M (2016 – 21)[23]	Hit-to-lead to end of Phase 1
GAMRIF†	£50M (2013 – 21)[24]	Discovery research to end of Phase 1
GARDP	€270M (2017 – 23)	All stages & patient access
Global AMR R&D Hub	€500M (2018 – 2028)[25]	AMR research coordinator (initial focus)
IMI ND4BB	€650M (2014 – 20)[26]	Entire value chain
JPIAMR	€234M (2012 – 24)	Discovery research

NIH†	$2,002M (FY2014 – 18)[27]	Discovery research to Phase 2
REPAIR	$165M (2018 – 23)	Lead optimization to end of Phase 1
Wellcome Trust†	$155M (2016 – 21)[28]	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 £20 toward CARB-X over three years.[29] Wellcome Trust is directing $155M toward CARB-X over five years.

In addition to mechanisms that provide research and development support, there have been efforts to improve the regulatory pathway for antibiotics. 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.

Although push incentives have effectively supported early-stage antibiotic development and its financing, distinct market challenges discourage later-stage product development, registration, and commercialization. First, although designed to slow AMR, widespread antibiotic stewardship programs limit the unit-sales that provide antibiotic revenue in FFS payment systems for drugs. Second, regulatory approvals based on non-inferiority trials do not provide comparative effectiveness evidence to justify rapid uptake and higher payment of new antibiotics when they reach the market. This initial evidentiary gap limits manufacturers' ability to set prices adequate to sustain continued innovation and evidence development. Furthermore, even if new antibiotics are eventually determined to be safer or more effective than generic alternatives, widespread use is delayed until data regarding their effectiveness and susceptibility to resistance is collected and disseminated. Third, 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 developers could benefit from financial support during later-stage development and following the approval of a new antibiotic.

Pull Incentives for Antibiotics

To date, GAIN's provision awarding eligible QIDPs five years of additional market exclusivity is the only established pull incentive. While some developers have found the incentive useful, for products with low sales, additional market exclusivity is unlikely to significantly augment revenue.

As a result, many stakeholders are expressing renewed urgency around the development of effective pull incentives. Several mechanisms have been proposed, including the advanced market commitment (AMC), priority review voucher (PRV), transferrable exclusivity voucher (TEV), and market entry reward

(MER). Among them, the TEVs and MERs are viewed as attractive pull mechanisms for antibiotics, whereas AMCs would need to be constructed so that they were not dependent on unit sales (like MERs) and PRVs may not generate sufficient revenue for antibiotic developers. TEVs are attractive because they could generate substantial revenue by extending the market exclusivity of an existing product. A TEV has the potential to drive value for both large and small developers and maintains budget neutrality. However, higher prices on existing drugs raises concerns about the affordability of current high-cost treatments, and so legislative proposals to implement TEVs for antibiotics 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 (Table 5).[2] Such a reward would likely take the form of multiple annual payments to a developer following the approval of a new antibiotic. To ensure the availability and stewardship of a new antibiotic, payments would be contingent upon contractual conditions between the payer and developer. These payments would likely occur either 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.

Table 5. Recent Global Policy Proposals to Support Antibiotic Development. Information modified from a March 2019 Needham & Company, LLC report.[32]

Proposal	Push or Pull Incentive	Date Last Introduced	Details
United Kingdom's National Action Plan	Pull (payment changes)	January 2019	Subscription model with 2-3 antibiotics (set fee for unlimited access to drugs) and an antibiotic investment charge
DISARM	Pull (payment changes)	December 2018	Changes to FFS reimbursement; allow Medicare to offer an add-on payment for certain antibiotics
Transferable Exclusivity Voucher	Pull (reward)	June 2018	A company that successfully develops a high priority antibiotic would receive a voucher that grants 12 months of transferable exclusivity to a drug of the company's choice.
DRIVE-AB	Pull (reward)	January 2018	Public-private consortium with 23 entities across Europe including a central collaboration hub to coordinate push and pull mechanisms and $1B market entry award
Duke-Margolis PAVE Award	Pull (reward with payment changes)	August 2017	Market entry reward upon regulatory approval spread over 5-6 years, with the largest in year 1, and additional revenue from value-based contracts with payers
BCG and German Federal Ministry of Health report, "Breaking through the Wall"	Push and Pull (reward)	February 2017	Recommendations included the need for target product profiles, a global research fund, and a global launch award.
The Review on Antimicrobial Resistance	Push and Pull (reward)	May 2016	Invest in a spectrum of activities to support antimicrobial development, including global innovation fund, large

			market entry reward, and diagnostic market stimulus.
GAIN Act	Pull (payment changes)	2012	Provides five years of additional marketing exclusivity for Qualified Infectious Disease Products (QIDP). It also provides qualifying products fast track and priority review status for regulatory review.

Linking Antibiotic Value and Policy Implementation: Market Entry Rewards and Complementary Payment Reforms

Implementing a successful and sustainable pull mechanism, such as a MER, will require policymakers 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 antibiotics 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. By multiple estimates, MERs designed to attract larger developers will need to offer around $1 billion worldwide, excluding revenues.[2] 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 potential new antibiotics are eligible for a MER, they may also consider how existing drug payment reforms could also help support antibiotic availability. Furthermore, developers awarded an entry reward will be expected to maintain the production and supply of their new antibiotic, and stable patient access. How eligibility criteria are determined and obligations between funders and reward recipients are structured is a matter of current debate. However, if implemented thoughtfully, many stakeholders agree that MERs may indeed help to revitalize the antibiotic industrial base.

Duke-Margolis Workshop

The goal of this workshop if to better define the economic rationale for large scale investment in pull incentives for antimicrobials and to drive consensus on the better approaches for implementations, with a focus on ways that the US government can contribute. During this workshop, the following topics will be discussed:

Characterizing the Economic Value of New and Novel Antibiotics for Priority AMR Threats. A number of factors comprise the value of an antibiotic, and unlike drugs for many other conditions, many of these are related to external public health benefits. It can be difficult to estimate the value of many of these benefits. This session will focus on characterizing and quantifying the components of antibiotic value from an economic and public health perspective. Discussion will address the following:

- Approaches and data needed to model distinct aspects of antibiotic value, including insurance, contagion, and public health value
- The potential impact of novel antibiotics on these costs and outcomes in the healthcare system

- Components of value are most salient to policymakers and how to develop a more informed value case

Bridging the revenue gap between market forces and investment. The current market for novel antibiotics is not attractive for developers, and as a result, there is less investment from large companies, venture capital, and their shareholders. This session will explore the magnitude of return that is expected from private investment dollars, actual returns on novel antibiotics, and how a pull incentive could bridge that gap between antibiotic value and current financial expectations. In this session stakeholders will:

- Explore how the market values novel antibiotics, including potential returns based on current utilization rates
- Discuss from an investment perspective, which characteristics of novel or future antibiotics influence their valuation most and contribute to risk
- Assess generation of returns through drug pricing vs. pull incentive
- Consider how a large pull incentive could complement or interact with existing incentives

Market Entry Rewards—Eligibility & Implementation. Options for how a large pull incentive could be implemented are numerous and will differ based on the desired objective. In addition, there will be both practical and political challenges to taking action. This session will explore:

- Implementation steps with emphasis on political and practical feasibility
- How identified areas of antibiotic value could contribute to reward eligibility
- Potential funding mechanisms and complementary payment reforms for a market entry reward
- Outcomes that could be used to measure the success of a pull incentive in reinvigorating the antibiotic market

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