

Value-based strategies
for encouraging new
development of
antimicrobial drugs

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Executive Summary

Resistance to current antimicrobial drugs is a growing source of morbidity, mortality, and healthcare costs. Challenging market dynamics have led to a weak pipeline of drug candidates to respond to these threats. Combined, these two trends represent a significant and growing threat to US and global health preparedness.

Most companies have exited the antimicrobial market, and those that remain are working on a small number of drugs. Low return on investment (ROI) relative to broad public health benefits is a major contributor to the sparse pipeline of drugs targeting multidrug-resistant organisms that pose serious public health threats. Low ROI is driven largely by appropriate antimicrobial stewardship programs (ASPs) that limit the use of innovative therapies to appropriate patients, availability of effective and low-cost generics for typical infections that limit novel antimicrobial use, and a reimbursement system that does not reflect the true public health value of effective drugs for multidrug-resistant organisms. In particular, antimicrobials for high-priority, resistant organisms have a public health value that far exceeds the fee-for-service (FFS) payment for the patients who actually have resistant infections. Rather, their value includes being available for use when necessary to stem the spread of resistant microbes before they take hold. Because of these challenging market conditions, a wide range of global experts (including Chatham House, the AMR Review in London, and the DRIVE-AB consortium in the E.U.) have recommended much stronger market entry or “pull” economic incentives to encourage investments to bring such antimicrobials to market.

However, these approaches have not yet taken hold. The public investment required is daunting at a time of increasing fiscal pressures. Moreover, bringing a product to market does not assure its continuing availability and appropriate use. Further, the U.S. health care system relies on multiple private payers as well as public financing, and a public funding approach might crowd out private spending and delivery systems.

The Duke-Margolis Center for Health Policy is developing U.S. policy approaches that could provide better economic incentives to antimicrobial developers that successfully bring effective drugs to the market, providing a societal benefit that exceeds the cost of the incentive. Working with a broad-based advisory group, Duke-Margolis has developed a proposal for a publicly-leveraged, value-based payment model to address these challenges in a U.S. context. The Center based its work on several principles: be part of a comprehensive strategy; promote innovation, access, and stewardship; be sustainable and predictable, leverage public money with private funds; provide rapid access to funds upon market entry; and align with broader shifts in the U.S. healthcare system to value and quality.

Our Priority Antimicrobial Value and Entry (PAVE) Award proposal combines a market entry reward with population-based payments from public and private payers that phase in over time. The market entry reward provides funds over early years of marketing after FDA approval. Subsequent payments rely on the developer to increase revenue from population-based contracts with payers that are linked to value to society through infection prevention, availability, support for sustainable use, and continued data collection. By leveraging both public and private support, the PAVE Award provides developers with quick access to a significant reward upon market entry as well as strong incentives for manufacturers to engage with payers in shifting reimbursement from FFS to population-based contracts that support high-value, sustainable use. The PAVE Award’s risk-sharing model delinks ROI from volume use to reward and support availability and appropriate use of effective antimicrobials. This model addresses the fundamental need for public investment in drugs that combat resistant bacterial infections by resolving

the current conflict between the drivers of ROI and strong stewardship programs, while reinforcing the “volume to value” shift in health care payments, and leveraging, rather than replacing, private financing. Finally, the model can complement and build upon approaches supported by private foundations, other countries, and multinational organizations to further generate global support for the development of priority antimicrobials.

Overview

Increasing antimicrobial resistance (AMR) is a serious and growing global public health threat. In the U.S. alone, these infections affect more than two million people annually, cause an estimated 23,000 deaths, and generate an estimated economic burden exceeding \$55 billion.¹ If current trends continue, 300 million people worldwide are expected to die prematurely in the next 35 years due to antimicrobial resistant infections.²

Inappropriate use of existing antimicrobials contributes to the development of AMR. One third of the 266.1 million courses of antibiotics dispensed to outpatients in the U.S. in 2014 were either unnecessary or inappropriate, at a direct cost of over \$1 billion per year.^{3–5} Further, the IMS Institute for Healthcare Informatics estimates that antibiotic misuse leads to more than \$35 billion in avoidable costs. High prescription rates for broad-spectrum drugs further contribute to AMR by increasing the selective pressure on all bacteria to develop broader resistance. Unfortunately, limited development and adoption of effective and rapid diagnostic tools in clinical practice hinders the use of narrow-spectrum antibiotics, which target groups of bacteria more selectively.

In 2013, the Centers for Disease Control and Prevention (CDC) released a report detailing the most urgent resistant bacterial threats to public health.⁶ Additional types of infections are facing a dwindling number of treatment options, and the World Health Organization (WHO) independently identified twelve priority bacterial pathogens that should become the primary focus of research and development (R&D) efforts.⁷ Although the public health threats and R&D priorities have been identified, the pipeline of potential treatments is limited, highlighting the need for policies that provide financial incentives to support development and availability.

This paper describes how to stimulate investment in development and appropriate use of high priority antimicrobial drugs, including a new proposal that reflects U.S. and global trends toward value-based, not volume-based payment systems. Our recommendations reflect work guided by a multi-stakeholder Advisory Group that includes representatives from private and public payers, pharmaceutical companies of all sizes, professional societies, academic researchers, think tanks, government agencies* and patient advocacy organizations, as well as through interactions with stakeholders during an expert workshop and public meeting.

The Problem

WEAK ANTIMICROBIAL PIPELINE WITH LOW RETURN ON INVESTMENT RELATIVE TO PUBLIC HEALTH VALUE

A vibrant and innovative antimicrobial drug pipeline is needed to address the growing public health threat of resistant organisms, yet a small number of candidates are in development. Of the approximately 40 potential drugs in clinical development, only sixteen are targeted toward “urgent” pathogens and, based on typical attrition rates across drug development, only six of these sixteen are expected to be approved between 2017 and 2024.^{8,9} In comparison, more than 170 drugs for diabetes and more than 700 for cancer are in various stages of clinical development.^{10,11}

* e.g., the Biomedical Advanced Research and Development Authority (BARDA), the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA)

One reason for the limited pipeline is the relatively high cost and difficulty of developing antimicrobials and demonstrating their effectiveness. Drug development in many clinical areas is expensive and risky; estimated costs across all areas range up to \$1.2-\$2.6 billion for novel drugs, and it takes roughly 8 years for market approval from initial IND filing, with an overall success rate of 10 percent.^{9,12,13} But there are other particular market-related challenges that lead to inadequate investment in antimicrobial research and development.

REIMBURSEMENT FOR HIGH-PRIORITY ANTIMICROBIALS DOES NOT REFLECT PUBLIC HEALTH BENEFIT

Alongside substantial development costs and uncertainty, the financial rewards for bringing priority antimicrobials to market are low. Product developers evaluate market opportunities based on Net Present Value (NPV) analysis, which compares the investment to get a drug to market with the projected future returns in today's dollars. A 2014 study from the Eastern Research Group calculated a NPV for antimicrobial drugs in the range of -\$4.5 million to \$37.4 million, mainly due to limited market revenues.^{14,15} Between 2011 and 2015, the median yearly sales of brand-name antibiotics with unexpired patents ranged from \$24 million to \$75 million (Appendix 1)*, compared to more than \$500 million for most brand-name oncology drugs approved during the same period.¹⁶ Among the sixteen new, brand-name antimicrobials approved since 2000, only five have generated annual sales of more than \$100 million*. Blockbuster drug status requires annual sales over \$1 billion; antibiotics struggle to reach 10 percent of that goal. A NPV of \$200 million generally has been viewed as a benchmark above which companies might deem investment worthwhile, although this benchmark may vary by size and type of company.¹⁷

In contrast to returns for innovative therapies for non-communicable diseases, the market returns to antimicrobial developers are low relative to the potential benefits to society because those who use the drug are not the only beneficiaries of treatment. Rather, benefits of these drugs accrue to those who never need treatment, because the availability of the antimicrobial prevents the spread of the resistant organism. The people who benefit from avoiding infections through availability and appropriate use of an effective drug provide no revenue for antibiotic manufacturers. Accompanied by strong attention to limit antimicrobial use to appropriate cases — since use drives resistance, overuse drives resistance more rapidly — few individuals will ever develop a serious resistant infection. Ideally, the availability of these high-priority treatments would be accompanied by strong infection control and stewardship programs, to minimize the need for their use. For non-communicable diseases like cancer, the main value of treatment is limited to the actual individuals who are at risk for or who develop the disease.

Health care payments focus on the individuals who receive treatment. Payers and patients consider the value of treatment to their individual cases, not the broader benefits and cost savings to the infections that are prevented. As a result, especially when used appropriately, antimicrobials for high-priority infections are generally low-revenue products.

EVIDENCE OF SUPERIORITY FROM CLINICAL TRIALS IS NOT ROUTINELY FEASIBLE

New antimicrobials usually will not come with evidence demonstrating superior outcomes compared to standard of care.¹⁸ Although new antimicrobials will have preclinical in vitro and in vivo data showing their activity against bacteria that are resistant to other drugs, demonstrating this microbiological

* Derived from publicly available sales data 2010-2015

superiority in studies of humans is not possible routinely. The lack of clinical superiority evidence is due to both practical constraints in antimicrobial clinical trials and the desirability of minimizing the rate of infection due to highly resistant bacterial strains. Instead, most antimicrobials have been, and will continue to be, studied using non-inferiority trial designs in which the new agent is compared to another drug expected to also be active. Ethically, the comparison arm in a trial must be a regimen that represents what the treating physician thinks is the best course of treatment to cure the infection. Assuming there is an effective antimicrobial drug or regimen effective against the bacteria under study and because the outcome of interest is binary (cure vs no cure), the expected treatment effect for most novel antimicrobials is, at best, a cure rate that is no worse than usual care.

Further, if a large clinical trial could be designed to focus on a specific bacterium for which there are no effective therapies, then that would indicate a failure of policies to prevent the emergence of a widespread resistant microbe. If accrual of substantial numbers of patients into such a trial were possible, it would imply a situation with grim public health implications.

From the perspective of payers focused on value for an individual patient, a desire for demonstration of superiority is understandable to justify coverage and reimbursement of new antimicrobials at higher prices. But this perspective does not account for the public health goal of providing robust availability of antimicrobials when the routinely viable path for regulatory approval cannot be expected to produce such evidence.

DIAGNOSTIC UNCERTAINTY LIMITS APPROPRIATE USE

A lack of sensitive, specific, and rapid diagnostics leads to challenges both in clinical use and in antibiotic development. In day-to-day practice, acute infections require immediate treatment, but determination of the specific cause of the infection is surprisingly difficult. This paradoxical problem arises because the organisms which are commonly part of the healthy human microbiome are very often the same organisms which can cause infection and mere detection of a potential pathogen does not mean that it is causative. As a result, physicians often opt for relatively broad empirical therapy rather than narrow(er) therapy, and most often newer and novel therapies, based on diagnostics tests. Negative results (lack of detection of a pathogen or lack of detection of resistance) are results that are particularly likely to be ignored if the patient has significant risk factors for such infections.

Lack of available rapid diagnostics can also pose a challenge in antimicrobial clinical trials, particularly when a trial seeks to study infections due to a specific bacterium. If a patient is potentially suitable for such a clinical trial but the physician is unable to confirm this promptly with a test, the patient may be treated with one or more antibiotics prior to enrollment, which confounds examination of the treatment effects of the new drug under study. Further, if a patient is ultimately found to not have been infected with the target organism (without a rapid diagnostic this would be unknown at enrollment), but is enrolled in the trial because empiric evidence suggests that he may be, the sponsor will have spent additional time and money for data that will ultimately not contribute to drug approval. Both scenarios significantly increase inefficiency.

APPROPRIATE STEWARDSHIP MEANS LOWER VOLUME

Novel antimicrobial drugs must be used appropriately to slow the development of resistance. In healthcare settings, this goal is accomplished through ASPs with the core elements (defined by the CDC) of leadership commitment, accountability, drug expertise, action, tracking, reporting, and education.¹⁹

Stewardship plays a critical public health role by conserving new drugs for resistant infections; however, this practice also limits sales volume and ROI for new antibiotics. Appropriate stewardship also means that most novel antimicrobials have a narrow set of patients for whom they may be clinically appropriate, limiting use. In the U.S., the Centers for Medicare and Medicaid Services (CMS) has mandated stewardship programs as a condition of participation in Medicare for nursing homes, and issued a proposed rule to require the same conditions within hospitals. The CDC has set targets to reduce inappropriate antibiotic use in the outpatient setting by 50 percent and within hospitals by 20 percent. Both actions are excellent public health measures, but both accentuate the difficulties of a volume-based sales model for antibiotics. These measures can be reinforced by financial incentives: reasonably effective generic drugs are available for most infections, so that payers and patients should prefer these alternatives to high-priced new antimicrobials.

FEE-FOR-SERVICE PAYMENTS FAIL TO ENCOURAGE APPROPRIATE USE

The U.S. healthcare system relies on FFS payments. This payment system is a poor fit for antimicrobials because volume-based payments are fundamentally in conflict with stewardship to avoid the use of valuable antimicrobials when not needed to deter the emergence of resistance. As an alternative to pressures from manufacturers (and potentially patients) to increase utilization, a payment approach that delinks revenue from volume of sales could provide better incentives for appropriate use. In many areas of U.S. healthcare, the shift from volume- to value-based reimbursement is encouraging more appropriate treatment. But such payment mechanisms have generally not been used for antimicrobials.

CONSEQUENCES OF INADEQUATE MARKET REIMBURSEMENT FOR DEVELOPMENT

Failure of current payment systems to recognize public health benefits, pressures for appropriate stewardship, and the insufficient implementation of new diagnostics to aid identification of the right drug for the right patient at the right time all result in low revenues for antimicrobial developers, resulting in many companies leaving the antimicrobial space. Remaining small and medium companies struggle with securing funds from investors, and large manufacturers with a diversified pipeline struggle to justify investing R&D dollars in an area with an unpredictable and low return compared to other opportunities. These low revenues have led many larger drug developers to shift their discovery and development efforts to more lucrative areas. For example, AstraZeneca recently sold its late-stage antimicrobial portfolio to Pfizer and spun off its early stage work to focus on developing medicines in three focused areas, including oncology.²⁰ In 2014, one of the world's largest private antibiotic R&D efforts was at Cubist Pharmaceuticals. After being acquired by Merck, the vast majority of the Cubist R&D effort was shut down.²¹ Of the top 50 pharmaceutical companies (ranked by global sales), only five have antibiotics in clinical development.⁸

Efforts to improve antimicrobial development

GLOBAL “PUSH” AND “PULL” INCENTIVES

To address these issues, many global efforts have proposed economic incentives to stimulate and reward innovation, which include “push” and “pull” incentives. “Push” incentives focus on reducing the R&D costs for new antimicrobials by providing financial and infrastructure support. “Pull” incentives reward manufacturers after an antimicrobial enters the market, increasing potential revenue.

Chatham House, a London-based public policy institute, published a report in 2015 proposing antibiotic incentives spanning the entire development pipeline.²² Recommended pre-clinical and clinical trial push incentives include public funding to support initial discovery research, and tax credits, cash rewards, and public-private partnerships to reduce clinical trials and development costs, as well as a market entry reward (MER) that would reduce the manufacturers' dependence on sales volume for ROI (also known as "delinkage").

In May 2016, the Review on Antimicrobial Resistance (AMR Review), commissioned by the U.K. Prime Minister and supported by the Wellcome Trust, published a detailed proposal to combat antimicrobial resistance including an Innovation Fund to support for early-stage development of antimicrobials and a lump-sum payment MER to developers of antimicrobials meeting a defined clinical need.²³

In June 2016, DRIVE-AB, an EU initiative comprised of 23 public and private partners, released a preliminary report detailing five promising incentives for antimicrobial innovation: 1) grants for early stage research; 2) establishing a non-profit developer who would manage and finance discovery through commercialization; 3) a MER to developers following approval of an antimicrobial that meets certain criteria; 4) an "annual license fee" to drug developers for access to a specified volume of antimicrobials addressing unmet medical needs; 5) a dual-pricing model that charges a higher price for inappropriate use.²⁴ Final recommendations from DRIVE-AB will be released later in the year.

In September 2016, stakeholders from the pharmaceutical industry put together a Roadmap for Progress on Combatting Antimicrobial Resistance, which followed up on the previous Davos Declaration that was signed by over 100 companies and associations.²⁵ Recommendations included reducing the environmental impact of antibiotic production, encouraging appropriate use of antibiotics, improving access to antimicrobial products, and generating new opportunities for collaboration across industry and public sectors, which includes support for lump sum payments upon market entry.

The Boston Consulting Group (BCG) completed a study for the German Global Union for Antibiotics Research and Development (GUARD) Initiative in February 2017.²⁶ Two recommendations targeted research and development through the generation of Target Product Profiles to guide decisions for preclinical research, and a Global Research Fund to be used to fund projects, increase the community of antibiotic researchers, and support infrastructure. Two additional recommendations included a Global Development Fund to support clinical research, and a Global Launch Reward, a MER, with built in sustainability mechanisms for the company to pay back the reward over time and under certain conditions.

GLOBAL SUPPORT FOR A MARKET ENTRY REWARD

All of these global efforts recommended some form of a MER, which is designed to pay for vital antimicrobial drugs with public funds. The MER provides substantial additional revenues to reflect public health value quickly after approval, and removes the need for volume sales, which helps the developer recoup investments. A form of 'delinkage', which removes the 'link' between development costs and revenues, the MER enables uncoupling of the ROI from the volume of drug sales. Delinkage could benefit the antimicrobial market by removing dependence on sales to drive ROI, providing reimbursement and revenue independent of sales volume, removing the need to set high prices, and providing support for appropriate use.

As generally described above, implementation of the MER would require the formation of a new entity such as a trust to oversee the reward and the management of the antimicrobial. The reward would replace existing payments for antimicrobials, be funded by public sources, and be managed through national or international contracts that would prevent marketing, promote sustainable use, and ensure access in low-resource countries. While funds may be distributed in a lump sum or yearly payments, current proposals envision payments over five years for meeting certain benchmarks. The antimicrobial MER would need to be large enough for the developer to recoup R&D investments and provide enough revenue to justify a more substantial commitment to this therapeutic area. Given the significant public health benefits from the development of priority antimicrobials, the recommendations have estimated the effective level of public payment to be between \$500 million to \$4 billion to achieve an NPV of \$200 million for R&D investment in a priority antimicrobial.^{14,23,27,28}

While the MER would provide a clear reward for developers, there are several challenges with this model. First, public funds are difficult to obtain and potentially subject to ongoing budgetary approval; the more such funds can leverage, not replace, existing payment sources, the more likely an effective MER can be implemented and sustained. Second, manufacturers have little to no incentive to remain engaged in the product life cycle after receiving the reward unless some sales volume incentive remains. Finally, if the payment for this drug was fully delinked from sales volume, then providers could potentially access the drug for free, a disincentive to stewardship. Proposals to address these issues include setting strict guidelines for reward eligibility and developing a provider pricing system to encourage stewardship. However, such oversight would add further administrative costs, and may not be effective.

U.S. INCENTIVES

The U.S. has been leveraging push and pull incentives to promote antimicrobial development. Table 1 summarizes the push incentives that have been proposed or implemented in recent years. The Limited Population Antibacterial Drug (LPAD) pathway, which was included in the 21st Century Cures Act (2016), provides the opportunity for more streamlined clinical trials and an expedited approval process for antibiotics that address unmet medical needs for limited patient populations, but does not address the problem of limited sales volumes leading to low expected ROI.²⁹

Table 1. U.S. Push Incentives for Antimicrobials

Initiative	Sponsor organization	Description
Grant funding	National Institutes of Health (NIH)	Funds awarded for basic research on bacteria and antimicrobials. In FY 2015, Congress appropriated \$100 million to NIH specifically for AMR research.
Broad Spectrum Antimicrobials Program	U.S. Biomedical Advanced Research and Development Authority (BARDA)	BARDA invests non-dilutive funding in a company's antibiotic portfolio to help companies through clinical testing.
CARB-X	BARDA, NIH & Wellcome Trust	Public-private partnership, which includes life science accelerators and research universities. Focusing on preclinical R&D, aims to broadly cultivate promising novel antimicrobial products that can be moved into clinical pipeline. \$450 million in committed funding 2016-2021, with every federal dollar leveraged by an equal amount in private funds. The initial group of funded companies were announced in March 2017.
Tax credits for research and development	Pending House bill, "Reinvigorating Antibiotic and Diagnostic Innovation Act"	Would allow companies to receive tax credits equaling 50 percent of clinical testing expenses for a qualifying infectious disease therapeutic or diagnostic.
Limited population antibacterial drug (LPAD) pathway	Section 3042 in "21 st Century Cures Act"	Allows antimicrobial drugs to be studied in smaller, less expensive clinical trials, which would expedite the approval of the drug, but would limit the eligible patient population.

In addition, the U.S. has implemented several pull incentives to provide a reward after the product has entered the market. The Generating Antibiotic Incentives Now (GAIN) Act (2012) extends the exclusivity period of certain antimicrobials by five years. In 2000, CMS launched the New Technology Add-On Payment (NTAP) program, which provides higher Medicare payments for new medical products that are deemed by CMS, through an application process, to lead to substantial clinical improvement. NTAP payments were not designed specifically for antimicrobials, and only one antimicrobial drug has been approved for this program due to a focus on non-inferiority clinical trials.

In March 2017 the "Improving Access to Affordable Prescription Drugs Act" was introduced in the House and the Senate, and a section of this bill describes a monetary prize that would be provided to antimicrobial developers who bring to market a qualified high priority drug in exchange for forfeiture of market exclusivity and reasonable pricing.^{30,31} These prizes would be paid out of a two billion dollar "Antibiotics Prize Fund". This proposal is similar to those that have been put forward for a MER, but it is unlikely to move forward due to the bill including additional recommendations with wide ranging implications across the entire healthcare sector.

Two further pull incentive proposals have attracted considerable attention. The first is the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act, which was first

The DISARM Act and Transferable Exclusivity Vouchers: An immediate impact

New legislative efforts focus on providing higher and more predictable reimbursement to new antimicrobial products, providing significant incentives for antimicrobial development. Both the TEV and the DISARM Act could be integrated with the Priority Antimicrobial Value and Entry Award proposal to leverage health plan payments and payment reform to promote availability and appropriate use of antimicrobials. Eligibility requirements within these legislative proposals would create criteria for eligibility and measures of appropriate use, as well as encourage surveillance reporting — important foundations for a more sustainable system for financing and using high-priority antimicrobials in the United States.

introduced in the House in 2015 and is intended to allow broader add-on Medicare payments for innovative antimicrobial drugs. While drugs need to receive specific approval from CMS under NTAP, DISARM drugs automatically qualify for additional payments if they treat infections caused by qualifying pathogens. These additional payments would eliminate the disincentive for hospitals to use high priced antimicrobials by offsetting the cost of the antimicrobial to the MS-DRG, and the payments could potentially support better tracking of antimicrobial resistance and use of priority antimicrobial drugs. However, this incentive still links revenue to sales volume, potentially creating incentives for overuse, and does not reward the public health value for the antimicrobial beyond the patients treated.

Another proposed incentive that would address the linkage of sales volume and ROI is the transferable exclusivity voucher (TEV).³² There are several advantages to the TEV, including the tangible return to the manufacturer and ease of implementation. Further, the TEV does not require direct government appropriations. However, the TEV is challenged by the fact that new revenues come from raising drug spending in other therapeutic areas by delaying generic entry. Further, the TEV itself does not provide any incentive for appropriate stewardship or continued availability of the drug over its life cycle. It would require strong administrative guardrails to address these concerns.

Path for accomplishing delinkage in the U.S.

CORE PRINCIPLES

The global proposals outlined above (Chatham House, AMR Review, etc.) represent important steps to promote development of new antimicrobial drugs. However, they may be infeasible for implementation in the U.S. due to multiple factors, including the lack of a single payer system, limited public funds, and active movement from volume to more population-based financing approaches across the U.S. health care system. In order to accommodate these unique factors while still aligning with global efforts to combat antimicrobial resistance, we have identified eight core principles to serve as a foundation for our proposal. These principles, while described in previous proposals, have additional components to reflect unique factors that affect the U.S. (sidebar).

As described above, several global organizations have proposed the use of public funds to spur innovation, but sole use of public funds is not a preferred option in the U.S. Instead, we propose a partial public contribution (reflecting public good, population health needs, and appropriate use) building on continued payments from multiple public and private payers. While these payers serve

Core principles for antimicrobial economic incentives

1. Be a part of a comprehensive strategy, which promotes development across the lifecycle of a drug, and enables the success of both small and large developers
2. Promote and reward innovation
3. Promote access
4. Promote stewardship so that antibiotics are sustainable over generations
5. Be sustainable and dependable over the long drug development cycle (at least a decade)
6. Leverage public funds with private payments
7. Provide developers with rapid access to funds upon market entry
8. Support and align with broader shifts in payment models to value and quality and away from volume and intensity

distinct populations with different benefit designs and other features, they are generally moving from volume to value-based payment models, which our proposal reinforces for antimicrobials.

The shift from volume- to value-based payment within the U.S. is supported by a variety of mechanisms, including Alternative Payment Models (APMs), which are aimed at reducing unnecessary health costs while sustaining or improving the quality of care. This shift is often implemented through partial or full episode-based bundled payments (e.g., one payment to all providers treating an episode of care), or per-patient payments (e.g., per-member per-month payment to a patient's primary providers). The Alternative Payment Model Framework from the Health Care Payment Learning & Action Network (HCP LAN) outlines a path to move from FFS to population-based payments.³³ Within this framework, the goal is to achieve payments that are partially or fully at the episode- or person-level for a population of patients.

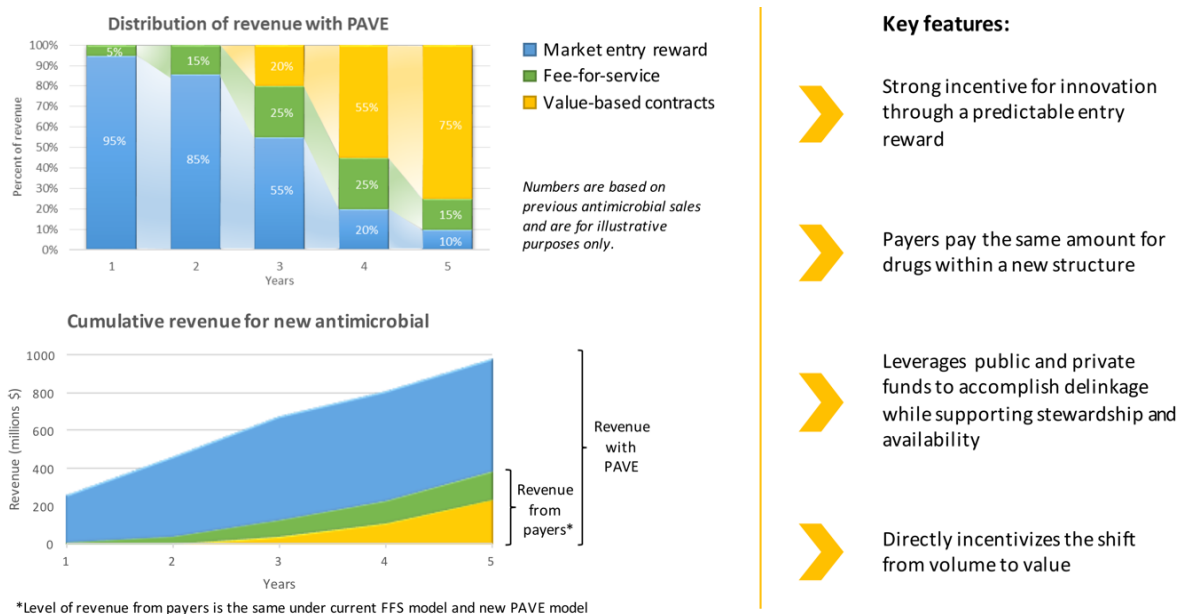
APMs are expanding in the U.S., and previous experiments have provided evidence of reduction in health costs, especially in controlling excess spending on inpatient care, reducing the average Medicare payment per episode by two to six percent each year.³⁴ The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 enables physicians and providers working with them to transition to payments based on quality rather than volume of care.

So far, there have been limited examples of the use of value- rather than volume-based payments for drugs, but some companies have entered into risk-sharing agreements based on the performance of the drug; for example, Amgen has negotiated deals with several payers for their PCSK9 inhibitor where payers are reimbursed a portion of the drug cost if agreed-upon performance metrics are not met. There are a range of operational and regulatory challenges to the implementation of such models that complicate their routine use, particularly in areas like antimicrobials that currently represent only a small part of health care payments. But antimicrobials may have the greatest benefit from a shift away from volume-based payment because of stewardship concerns. A shift from volume-based toward per-person payments for a covered population, as well as payments that are linked to measures of appropriate use and continued value, could provide much stronger incentives for appropriate use — and could be implemented in a manner that does not increase outlays for payers. Additional public market entry reward payments — to reflect the public health value of the antimicrobial — could reinforce this value-based payment structure. As we describe below, public support for market entry linked to this shift in payment could provide incentives for manufacturers to work with other stakeholders to help overcome the barriers to value-based payments for antimicrobials.

Priority Antimicrobial Value and Entry Award

To address the fundamental public health need for additional financial support for the development, availability, and appropriate use of high-priority antimicrobial drugs within the U.S. healthcare system, we propose a publicly-leveraged, value-based payment model. This model, called the Priority Antimicrobial Value and Entry (PAVE) Award, supports and rewards access to and sustainable use of innovative antimicrobial drugs, while protecting the public's health from resistant infections. The PAVE Award provides developers quick access to a significant reward upon market entry of an effective antimicrobial, and provides strong incentives to shift reimbursement from insurance plans to population- and value-based contracts, not payments based on volume of sales (Figure 1). The following sections describe the details of the model, which combines a version of the MER upon market entry with subsequent payments contingent upon demonstrating increasing revenue from value-based contracts with payers linked to availability, sustainable use, and continued data collection.

Figure 1. Outline of PAVE award



QUICK ACCESS TO FUNDS THROUGH A MARKET ENTRY REWARD

The first component of the PAVE Award, which is built upon the existing MER model, includes a publicly financed pull incentive, as has been recommended by multiple groups. This public funding would reflect a societal contribution to a global threat. In the PAVE Award, the MER component would be available over the first few years upon market entry for a very limited set of high priority antimicrobials with specific eligibility criteria to give manufacturers clear development goals, and the magnitude of the MER could increase if the drug meets additional, desired characteristics that are beneficial to larger public health needs, such as a novel mechanism of action, oral availability, or new class of drug.³⁵ This phase of the PAVE Award would provide developers predictable revenue, contingent on the drug's market availability, lack of prolonged shortages, or failure to meet the conditions for supporting a shift to sustainable payment described below.

The MER would need to be large enough to justify a commitment to antimicrobial development, but must also be sustainable. While the Center supports the concept of a substantial entry reward for a product that meets the eligibility criteria, we favor an approach that doesn't completely rely on the reward, to ensure that the majority of the revenue from payers shifts to alternative payment models that promote appropriate stewardship. FFS payments for these high-priority antimicrobials are only adequate if there is a high prevalence of highly resistant infections, which would be devastating from the public health perspective.

TRANSITIONING TO PAYMENTS THAT SUPPORT VALUE

The first component of the PAVE Award differs from the traditional MER by providing annual payments, with the largest portion paid in year one, and with significant but declining payments through years five or six as direct payments for drug availability and use ramp up. The magnitude of these payments will vary depending on the drug, with those drugs that represent a higher societal value receiving larger payments.

The second component of the PAVE Award directly incentivizes the company to wean off the MER through declining payments through years five or six, with each year's payment contingent upon developers demonstrating an increasing share of their revenue from population-based APMs linked to value to society through availability, support for sustainable use, and continued data collection. This transition would ensure that drug sales shift to APMs delinked from volume. The specific APM payment terms and overall payments will continue to be determined through contract negotiations between the manufacturer and payers, supported by measures that reflect value and stewardship in the covered populations (Figure 1).

While these contracts would provide a predictable and sustainable source of revenue for antimicrobial developers, it is important to emphasize that it will not result in higher drug costs to payers; rather, it creates incentives and opportunities for them to pay differently. These new contracts would not require payers to pay more than in FFS models, but would structure payments with a greater emphasis on public health in return for access to the drug. As the infrastructure for value measurement grows, developing these contracts will be easier and gain more widespread acceptance.

Such value-based arrangements might involve a payment to the manufacturer for access to the drug regardless of the number of units utilized; payments would be tied to value to the covered population rather than volume of sales. If stewardship protocols are in place and transmission of resistance is contained, low drug utilization would be expected, but having a drug for a low prevalence infection would be highly valuable. For example, a manufacturer might contract with a health plan on a "per member per month" (PMPM) basis for providing the drug when needed. A manufacturer might also enter into episode-based payment contracts to provide the drug as needed for all hospitalized patients in certain DRGs. In both cases, the contracted payment would not depend on the volume of the drug actually used. Rather, the per-member or per-episode payment would vary based on measures of, for example, appropriate use or continued effectiveness of the antimicrobial. Payments might also be tied to the development of better data and evidence on the benefits and risks of the drug, which could support better payment contracts in the future. In the case of inpatient drugs or physician-administered drugs for Medicare beneficiaries, this reform could be supported by the development and adoption of Medicare APM pilots by the Center for Medicare and Medicaid Services that could align with the private APM contracts.

Implementation issues

DETERMINING ELIGIBLE DRUG CANDIDATES

The PAVE Award model is intended to promote development and sustainable use of high-priority drugs that contribute to the reduction of drug resistant bacteria, and the incentive criteria should be tailored specifically to meet these needs. Target product profiles could set clear expectations of the desired drug characteristics that are required to qualify for the PAVE Award, laying out expected antimicrobial activity and other performance standards for the drug. Such eligibility criteria would benefit from further development, both in the U.S. and internationally. Near-term versions of PAVE payments could be awarded to drugs that meet existing criteria related to the public health benefit, such as oral forms that could be used more easily to control an outbreak early or a novel mechanism of action that could plausibly support new types of antibiotics for which resistance has not developed.³⁵ The WHO and CDC lists offer a good starting point for prioritizing pathogens that the drugs should target. CARB-X, the leading public-private partnership supporting pre-clinical antibiotic R&D, uses these lists to prioritize investments. However, as new resistant bacteria emerge, the eligibility list will need to adapt to these changes, so the criteria will need to have built-in flexibility and will need to be updated on a periodic basis.

DEVELOPING EVIDENCE FOR VALUE-BASED CONTRACTS

Successful implementation of the PAVE Award will require cooperation between developers, payers, and providers. The contracts should encourage short- and long-term savings from reduced inappropriate use, as well as reduced infection-related costs, such as extended hospital stays, treatment complications, and additional infections.

As described above, demonstration of superiority during clinical development compared to other products is nearly impossible and undesirable for public health because increasing the number of people for whom these drugs are appropriate would mean that resistance and/or transmission are increasing. Continued development of effectiveness evidence in the post-market settings is equally challenging (the drug will be used sparingly limiting sample size, high risk infections with complicating comorbidities can lead to death even with the use of effective antibiotics). However, continued collection of data

Public-private partnerships provide accountability while supporting innovation

Public-Private Partnerships can deliver results that are superior to either government or private actors alone. CARB-X is a new public-private partnership providing push incentives for pre-clinical R&D to address the threats of antimicrobial resistance. Launched on August 1, 2016, CARB-X has now raised \$455.5 million in funding from BARDA, NIAID and the Wellcome Trust. The first 11 awards were announced in March 2017 (<http://www.carb-x.org/portfolio>), and three of these initial projects represent new antibiotic drug classes against Gram-negatives, seven have new molecular targets, four are non-traditional approaches, and all target CDC and WHO priority pathogens. These projects were awarded almost \$24M initially and up to another \$24M if milestones are hit. All awarded funds are matched with private money, with 30-50% cost-sharing.

CARB-X will only fund projects through phase I clinical testing, leaving significant scientific and financial hurdles to clear prior to approval. Many of these companies will rely on funding from investors, which will only be available if there is a clear and predictable path to ROI. Implementation of the PAVE Award would provide a predictable return, making the investment in antimicrobials more attractive. Like CARB-X, the PAVE Award will supplement public funds with private payers, leveraging both to support innovation.

on the use of novel antibiotics, outcomes (including safety outcomes), can benefit the healthcare community in better understanding the use in clinical settings and support sustainable use. Thus, ideal performance measures in these contracts would be based on evidence of a drug's availability, support for sustainable use, and continued data collection.

The Center recommends that, as in other areas of health care performance measurement, measures related to the value in practice of a priority antimicrobial drug should build on measures available today. There are some available measures that could be used as a starting point, including measures that would pertain to ongoing availability and utility access measures and use data, all of which can help to track appropriate stewardship. The CDC's Antimicrobial Use Option of the National Healthcare Safety Network is already available to hospitals to report antibiotic use data and could be used to track use nationally. Pairing the Antimicrobial Use option with its companion Antimicrobial Resistance Option could provide the type of data that would assist in monitoring new antibiotics.³⁶ A second set of measures could be related to data collection and evidence development, and could include execution of studies that better define safety and utilization patterns of an antimicrobial drug. Specifically, these measures could include the performance of patient population and susceptibility studies and cost-effectiveness studies that estimate costs to the payer if the drug were not available. Finally, contracts will take into consideration the supply chain and availability.

Effective stewardship measures are critical for the success of developers under these contracts. Providers will need to collaborate with manufacturers to demonstrate adequate performance on stewardship measures within provider APMs. APM contracts can be designed to balance over- and under-use incentives, for example, through a combination of per-member per-month payments and payments for actual use. So long as the payments were a significant shift away from FFS payments, manufacturers and payers could negotiate mixed models, where manufacturers and payers both face financial risk (e.g., a partial capitation payment, with some adjustments based on volume and performance). Indeed, a further advantage of the PAVE Award model is that the same kinds of appropriate use measures can be used by payers to support aligned, value-based payments for both manufacturers and providers. This payment alignment can support developers in working collaboratively with providers and patients to promote and ensure appropriate use, which is critical for the long-term sustainability of the antimicrobial supply and public health.

FINANCING MECHANISMS

Both the AMR Review and DRIVE-AB have suggested the use of public funds to finance MERs. Such funds could come from general government revenues, but dedicated funding sources have also been proposed to best reflect the public good of these drugs. The AMR Review suggested a "pay or play" model, in which manufacturers that are not invested in antimicrobial development would be charged a fee. Many therapeutic areas (including chemotherapy and surgery) are dependent on effective antimicrobials; consequently, drug manufacturers should contribute to antimicrobial development through investment in their own antimicrobial R&D or by paying a fee. Another proposed funding mechanism is a tax on all antibiotic use, effectively a "user fee" for access to antibiotics.^{37,38} The purpose of this tax would be to not only generate funds to reward antimicrobial development, but also to discourage inappropriate use of current antimicrobials by increasing the cost of use. The entry reward could also be funded through a yearly per member fee for all healthcare plans, which would serve to distribute the cost of development across society.

An alternate approach in the U.S. to relying solely on taxes and fees would be to rely on the sale of transferable exclusivity vouchers (TEVs), either alone or in combination with a smaller tax, as described above. Instead of being awarded to manufacturers who bring priority antimicrobials to the market, TEVs could be an expedient method for providing public funding for antimicrobial development. As described above, there are some undue consequences that could arise from such incentives, which could potentially be addressed by establishing guardrails to promote efficiency. Appropriate limits on the time and/or revenue generated by the TEV, along with sufficient support for patient assistance programs, would ease some of the negative impacts of shifting the financial burden from antimicrobial drugs to other disease areas (Table 2). Additionally, the voucher recipient should be obligated to provide notice of which drug will be receiving the extension four years prior to expiration of that drug’s exclusivity, which should be sufficient notice to alleviate the impact on generic manufacturers.³²

Table 2. Proposed “guardrails” for an antimicrobial transferable exclusivity voucher program³²

Challenges	Potential solutions
Increases cost in other areas of healthcare	Cap voucher (in value or duration)
Can negatively affect the generic market	<ul style="list-style-type: none"> Voucher will only be awarded to new drugs (not applicable for previously approved drugs) Company that will be using the voucher must declare which drug the voucher will be used on at least 4 years prior to exclusivity expiration
Does not encourage stewardship	Link quality reporting requirements (e.g., efficacy, length of hospital stay) to receipt of voucher
Could be poorly targeted to needed antibiotics	Limit eligibility to drugs that meet criteria set by public/private partnership group, which will identify unmet need based on periodic reviews of infection rate, resistance, and the drug pipeline

Ten years after implementation of voucher program, the GAO could conduct a study to determine the effectiveness of the vouchers and whether the voucher program should continue

Whatever financing mechanism is used, public investment is needed to support the public health benefits of antimicrobial drug development and availability that are not captured well in payments for actual use of the drug. While this public investment would support a benefit to all of society, given increasing fiscal pressures, it is critical to leverage any public funding to minimize the costs of these efforts to the public. The market entry reward proposed here builds on rather than replaces existing funding streams for antimicrobials, limiting the need for public funds.

CARE SETTINGS

Market challenges for antimicrobial development span the inpatient and outpatient settings, but most novel antimicrobials under development and especially those intended to treat the most urgent infections that would qualify for the PAVE Award would be used in the inpatient setting. However, the PAVE Award could potentially be applied over time, if needed to drugs in the outpatient setting. Product developers, payers, and providers are entering into more risk-sharing, outcomes-based models to help address product performance uncertainty and to help ensure better value for dollars spent. Future payment approaches for antimicrobials in this setting could leverage CDC tracking systems as well as appropriate use guidelines that have been issued by CDC and other groups to ensure appropriate prescribing and stewardship. The guidelines and outcomes governing the value-based payment model

for high-priority inpatient antimicrobials may need adjustments to be applicable in the outpatient setting. But we expect that the same principles and approach can be applied.

DRUGS FOR RARE INFECTIONS

Some antimicrobial-resistant infections are extremely rare. New antimicrobials that treat these infections are unlikely to generate significant costs for payers — and payers may not see the value in having contracts in place for their use. Creating value-based payment contracts — or any payer contracts — may not be worthwhile. In these cases where no consequential private market exists, as with drugs needed as countermeasures, a MER might be linked to appropriate access and continued evidence development. Of course, it will generally be in the manufacturer's interest to work out value-based contracts for priority antimicrobials whenever feasible, to provide additional revenue streams.

TRANSITION TO ROUTINE USE OF VALUE-BASED PAYMENTS FOR ANTIMICROBIALS

The presentation of our model focuses on the current status of fee-for-service payments for antimicrobials, recognizing that it may take several years to phase in the use of APMs based on value not volume of sales. With the incentives and momentum created by our proposed approach, the aim is to make value-based payment the norm for antimicrobial revenues. As these mechanisms become more routine, a larger share of revenues from value-based payments should be expected earlier after launch of a new priority antimicrobial that qualifies for the market entry payment. Legislation supporting this approach might even specify a transition path to the predominant or full use of value-based payments for antimicrobials, such that antimicrobials launched in, for example, 2027, would be expected to have a high share of value-based payment contracts in place from launch onwards.

Conclusion

Recognizing the importance of a robust pipeline of antimicrobial drug candidates to maintaining public health, the proposal described here is designed to provide a strong, leveraged financial incentive for priority antimicrobial development within the U.S. The PAVE Award and subsequent value-based contracts would build upon payment structures that are currently in place to shift the focus from sales volume to outcomes and appropriate use. This proposal will require collaboration across a range of stakeholders, all of whom will stand to benefit from the availability of effective, high-priority antimicrobials. While it may take several years to fully implement this proposal, the PAVE Award could begin making a major contribution now to the global effort to create and sustain a robust pipeline of antimicrobials to address urgent and growing public health needs. In particular, PAVE could be integrated with current legislative proposals for TEV and DISARM, using the TEV as the funding mechanism for the PAVE Award and implementing DISARM in a way that supports the transition to better payment models for availability and use of priority antimicrobials in hospitalized patients. With the growing threat of antimicrobial resistance, and the urgent need to develop a more sustainable way of assuring the availability and appropriate use of priority antimicrobials in the United States, the time for implementation is now.

Appendix 1. U.S. Net Sales of New-Molecule, Brand-Name Antibiotic Drugs Approved after 2000, in U.S. dollars (millions)

Brand Name	Molecule Name	Owner	Approval Year	SALES				
				2011	2012	2013	2014	2015
Avycaz	<i>ceftazidime/avibactam</i>	Allergen	2015	Product not yet launched				35.8
Sivextro	<i>tedizolid phosphate</i>	Merck	2014	Product not yet launched			2.4	37
Dalvance	<i>dalbavancin</i>	Allergen	2014	Product not yet launched			14.6	20.3
Orbactiv	<i>oritavancin</i>	Medicines Co.	2014	Product not yet launched			0.8	9.1
Difcicl	<i>fidaxomicin</i>	Merck	2011	24.4	74.4	51.6	47.7	39.8
Teflaro	<i>Ceftaroline fosamil</i>	Allergen	2010	2.7	22.4	44	70.3	118.5
Vibativ	<i>Telavancin</i>	Theravance	2009	10.0	0.0	0.0	4.4	9.4
Doribax	<i>Doripenem</i>	J&J (divested)	2007	Marketing and development halted in 2010				
Tygacil	<i>Tigecycline</i>	Pfizer	2005	148	152	150	112	110
Ketek	<i>Telithromycin</i>	Sanofi (divested)	2004	Off the market				
Cubicin	<i>Daptomycin</i>	Merck	2003	698.8	809.2	908	977	1127
Factive	<i>Gemifloxacin</i>	Vansen (Divested)	2003	6.3	0.36	-0.12	Divested the drug in 2012.	
Spectracef	<i>Cefditoren pivoxil</i>	Vansen (Divested)	2001	8.1	0.33	-0.72	Divested the drug in 2012.	
Invanz	<i>Ertapenem</i>	Merck	2001	406	445	488	529	569
Zyvox	<i>Linezolid</i>	Pfizer	2000	640	665	688	680	457.8

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