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Robert J. Margolis, MD
Center *for* Health Policy



Tracking the Progress of Economic Incentives for Antimicrobial Drug Development in the U.S. and Across the Globe

A landscape analysis to inform "Designing Economic Incentives for Antimicrobials: Implementation in the U.S. Context"

November 9, 2016

About the Duke-Margolis Center for Health Policy

The Robert J. Margolis, MD, Center for Health Policy at Duke University is directed by Mark McClellan, MD, PhD, and brings together expertise from the Washington, DC policy community, Duke University and Duke Health to address the most pressing issues in health policy.

The Center's mission is to improve health and the value of health care by developing and implementing evidence-based policy solutions locally, nationally, and globally. For more information, visit healthpolicy.duke.edu.

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Overview

Infections caused by antibiotic resistant bacteria result in approximately 48,000 deaths annually in the U.S. and E.U.¹, with the potential for far more infections and higher mortality if resistance rates continue to rise.² Antibiotic resistant infections are costly, with almost \$22 billion spent on direct and indirect costs in Europe and the U.S. annually.³ The public health burden and cost of these hard-to-treat infections could be significantly reduced if antimicrobial drugs were available to treat them. However, inappropriate use has reduced the effectiveness of currently available drugs, and the limited pipeline of drug candidates means there will be only a small number of products targeting a growing threat of antibiotic-resistant pathogens.

Factors contributing to limited R&D of antimicrobial drugs and the current lack of needed antimicrobials for certain multi-drug resistant infections include the technical challenges of developing safe and effective new products, as well as adverse market conditions, including competition with low cost generics limiting the market for new antimicrobials, low uptake driven by effective stewardship programs that limit use, and a fee-for-service (FFS) reimbursement system that does not reflect the true public health value of having well-targeted effective antimicrobial drugs.⁴ Because of these challenging conditions, stronger economic incentives are needed to reinvigorate the antimicrobial drug pipeline.

Global efforts are underway to address the problem. Initiatives have targeted antimicrobial development at all points in the drug lifecycle, with “push” incentives supporting early development, and “pull” incentives boosting return on investment. In the U.S., the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA) have implemented programs that provide funds for antimicrobial preclinical and early clinical development, while groups in Europe, such as Chatham House, the Review on Antimicrobial Resistance, and DRIVE-AB, have released proposals that aim to provide sufficient push and pull economic incentives to stimulate R&D and reward development of innovative products. A common thread in these proposals is the need for substantial pull incentives that provide revenue that is not driven by drug utilization and can enable efforts to appropriately target and limit the use of antibiotics. However, the so-called “de-linkage” proposals have come from global efforts, which may raise distinct questions about suitability and feasibility for implementation in the U.S. For example, the pluralistic nature of the U.S. system, with multiple public and private payers with different benefit designs, may not be well-suited to a unified, publicly-financed approach to delinking antimicrobial reimbursement from volume; at the same time, public and private payers are shifting from volume to value-based payment methods. In the United States, achieving the goal of more effective support for antimicrobial development and use may require distinctive approaches that fit the distinctive health care context.

The Duke-Margolis Center for Health Policy (the Center) has undertaken a project to develop policy approaches that de-link reimbursement from volume in the United States, including through alternative payment models. While notable progress on push incentives has occurred, and a comprehensive strategy should include both push and pull mechanisms, this initiative is focusing on feasible pull incentives. More specifically, the Center is working to develop a model that would provide rapid access to funds for developers upon approval of a drug addressing high-priority needs, that leverages any public funding with private support, and that promotes the shift from volume-based to value-based reimbursement.

The initiative reflects the work of a broad-based Advisory Group that includes representatives from private and public payers, small/medium as well as large drug manufacturers, professional societies, government agencies (i.e. BARDA, CDC, NIH, FDA) and a patient advocacy organization. The Center convened an expert workshop in July 2016 to explore the practical implementation challenges of several proposed antimicrobial economic incentives. With further research, guidance and feedback from additional stakeholders, including the Advisory Group, the Center is developing a set of

policy options for promising economic pull incentives, including a new proposal aimed at creating sustainable pathway for alternative value- and population-based payments for innovative antimicrobials.

As a foundation for further development of proposals to improve the returns to the development and sustainable use of high-value antimicrobials, this issue summary provides a landscape analysis of the factors that have led to the current state of drug development for antimicrobial resistance, reviews the organizations that have been convening on the issue, and describes a range of incentive proposals.

Introduction

Antimicrobial drug resistance (AMR) is a global public health threat driven by inappropriate use of existing drugs and a marked decline in innovative antimicrobial development. Patients and clinicians are increasingly confronting infections caused by pathogens, such as *C. difficile*, Methicillin-resistant *Staphylococcus aureus* (MRSA), and Carbapenem-resistant Enterobacteriaceae (CRE), which are unresponsive to many antimicrobial drugs. Antibiotic-resistant infections in Europe cause about 25,000 deaths annually, incurring about \$1.7 billion in direct and indirect costs. In the U.S., the Centers for Disease Control and Prevention (CDC) has estimated that antimicrobial drug resistant bacteria cause two million infections and 23,000 deaths annually, with estimated direct costs of \$20 billion.⁵ If antimicrobial resistance rates continue to rise, experts estimate that annual deaths worldwide will rise to 10 million by 2050.⁶

AMR is the result of a combination of factors. Antimicrobial overuse and misuse includes prescribing antibiotics for viral infections or for minor infections that will likely resolve on their own, patient non-compliance (e.g. not completing a full course of antibiotics as prescribed), and preventive use of antibiotics in clinical and agricultural settings. A recent study indicated that one in three prescriptions for antibiotics is inappropriate.⁷ Curbing these practices could significantly reduce health care costs, but will require public and provider education about proper use of antimicrobials and better support for appropriate prescribing. Novel drugs that target antibiotic-resistant pathogens are needed; however, antimicrobial drug development faces technical challenges in identifying new mechanisms of action to address evolving pathogens and significant challenges designing and carrying out clinical trials in the absence of effective rapid diagnostics.⁸ Additionally, there are market challenges that drive low returns on investment and disincentives for market entry including a) competition from low cost generic antimicrobials that remain effective enough for the vast majority of clinical applications, leaving a small portion of cases when the new drug is needed; b) low sales of the new antibacterial due to effective stewardship programs that limit use to protect the drug's utility; and c) relatively low prices in the context of a fee-for-service (FFS) reimbursement system that doesn't reflect the true public health value of having well-targeted effective antimicrobial drugs.⁹ Developing better economic incentives for the use and sustainability of novel and effective antimicrobials is a key element of addressing this challenge.

Antimicrobial-Resistant Bacterial Infections: A Growing Threat

The number of bacteria that carry some resistance to antibiotics has been increasing over the years. In 2013, the CDC named the top drug-resistant infections, and categorized them by urgency of the threat they posed [Table 1].¹⁰ One of the three most urgent threats is *Neisseria gonorrhoeae*, which is the bacteria that causes gonorrhea. Gonorrhea has developed resistance to available treatments over the last two decades. In the late 1990s and early 2000s, resistance to ciprofloxacin was detected in gonorrhea samples; by the mid-2000s, ciprofloxacin resistance was detected in more than 13 percent of infections, and resistant infections were present in all regions of the country.¹¹ As a result, cephalosporins became the recommended treatment for gonorrhea, but evidence of resistance to these drugs has also started to appear. Today, dual therapy is recommended for gonorrhea infections to try to slow additional drug resistance, but the number of drug-resistant cases continues to increase rapidly.¹²

Another group of bacteria on the CDC urgent threat list is Enterobacteriaceae family, which includes *Escherichia*, *Klebsiella*, *Salmonella*, and *Shigella* species. Some of these species overlap with the Gram negative bacterial species that make up the "ESKAPE" pathogens, which include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacter strains, which figure prominently in healthcare-associated infections (HAIs).¹³ HAIs frequently arise from ventilators, catheters, and surgery and they are a significant source of drug-resistant infections. In the U.S., more than 700,000 infections per year are acquired in a hospital, and of those, 1 in 7 are caused by a drug-resistant strain of Enterobacteriaceae, Enterococcus, *Staphylococcus aureus*,

Pseudomonas aeruginosa, or Acinetobacter.¹⁴ It has been reported that between 4-25% of patients harbor an infection that is resistant to commonly used drugs.¹⁵

The pathogens identified by CDC and others that make up ESKAPE represent an area of unmet medical need. In the past 20 years, drugs have been approved for only 15 of these 23 bacteria. Further, only 19 of the 37 antimicrobials in clinical trials are intended to treat either a CDC urgent threat or an ESKAPE pathogen.

However, there are scientific challenges that hamper the development of these drugs. Different antimicrobial drug classes target unique structures or bacterial processes that are vital to the bacteria’s survival. Due to structural differences, Gram negative bacterial infections are significantly harder to treat than Gram positive infections. Gram negative bacteria have a larger number and greater diversity of mechanisms that remove antibiotics from the cell, and they produce a wider variety of enzymes that destroy antibiotics.¹⁶ As a result, R&D is more difficult for Gram negative infections, and there are currently fewer treatment options on the market.

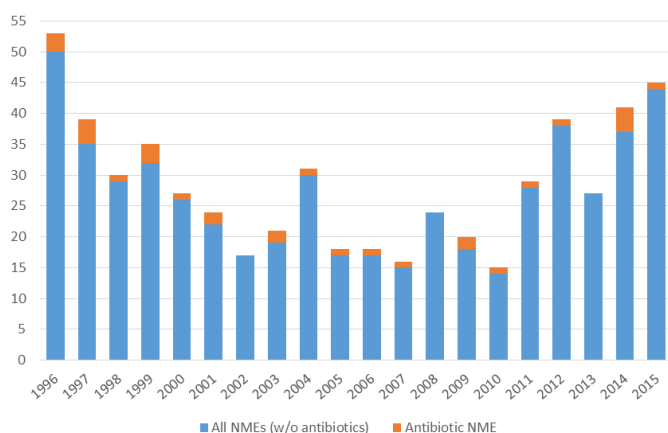
Narrow-spectrum antibiotics target a small subset of bacteria; they are a precision treatment for specific types of infections. However, a lack of diagnostic tools means that narrow-spectrum antimicrobials are used less frequently, leading to fewer incentives to develop precision drugs. As a result, broad-spectrum antimicrobials, which target a large variety of bacteria, are frequently used. Broad-spectrum drugs increase the selective pressure on all bacteria to develop resistance to the treating drug. An additional factor compounding the issue of resistance is that treating a susceptible infection with broad spectrum antibiotics may result in additional infections. As an increasing body of research has demonstrated, the non-pathogenic bacteria that occupy the human body play a beneficial role in keeping pathogenic bacteria at bay. Following treatment with broad-spectrum antibiotics, patients are more susceptible to the development of *C. difficile* infections, which are resistant to most antimicrobial treatments.¹⁷

Current Antimicrobial Market

Some have estimated that the cost of developing a new drug to be as high as \$2.6 billion, a number that accounts for failures along the way.¹⁸ Antimicrobial development is even more costly due to a lack of sensitive and rapid diagnostics, which makes evaluating a drug against a specific pathogen exceedingly difficult and time consuming. Because of the acute nature of infections, treatment must begin immediately. Without a clear diagnosis, patients will be treated empirically without confirmation of the actual infecting pathogen, and this treatment will confound the ability to enroll that patient in a clinical trial to examine the effect of the more targeted antimicrobial. While some of the clinical trial burden has been lessened by the release of FDA guidance advising industry on the use of non-inferiority trials to support approval of antibacterial drugs for serious infections, drug manufacturers encounter challenges when a new drug is approved and payers ask for evidence of superiority over other drugs to justify paying higher prices. This combination of factors means that the return on investment by a pharmaceutical company on an antimicrobial is likely to be significantly lower than a drug produced to target another disease. As a result, the number of new drugs developed by pharmaceutical companies, and the number of companies searching for new antibiotic candidates, has decreased over

Table 1: CDC Pathogen Threats
Urgent Threats (3) <i>Clostridium difficile</i> Carbapenem-resistant Enterobacteriaceae <i>Neisseria gonorrhoeae</i>
Serious Threats (11) Multidrug-resistant Acinetobacter Drug-resistant Campylobacter Extended spectrum Enterobacteriaceae Vancomycin-resistant Enterococcus Multidrug-resistant <i>Pseudomonas aeruginosa</i> Drug-resistant non-Typhoidal Salmonella Drug-resistant Salmonella serotype Typhi Drug-resistant Shigella Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) Drug-resistant <i>Streptococcus pneumoniae</i> Drug-resistant Tuberculosis
Concerning Threats (3) Vancomycin-resistant <i>Staphylococcus aureus</i> Erythromycin-resistant group A Streptococcus Clindamycin-resistant group B Streptococcus

Figure 1: Number of new molecular entities (NMEs) approved by the FDA, 1996-2015



the years. With the exceptions of 2009 and 2014, in most years over the last decade, only an antimicrobial drug has been approved each year, with only 12 antimicrobial drugs approved in total [Fig 1]. This is half the rate of approval compared to 25 years ago, when 24 antibiotics were approved between 1988 and 1997.¹⁹

Of the top 50 pharmaceutical companies (ranked by global sales), only five have antibiotics in clinical development, and between 2010 and 2015, only one of eight drugs was produced by a top sales company.²⁰ Several start-up companies have begun to enter the antimicrobial field, with some success. While new companies may be filling some of the development shortfall, smaller or start-up companies

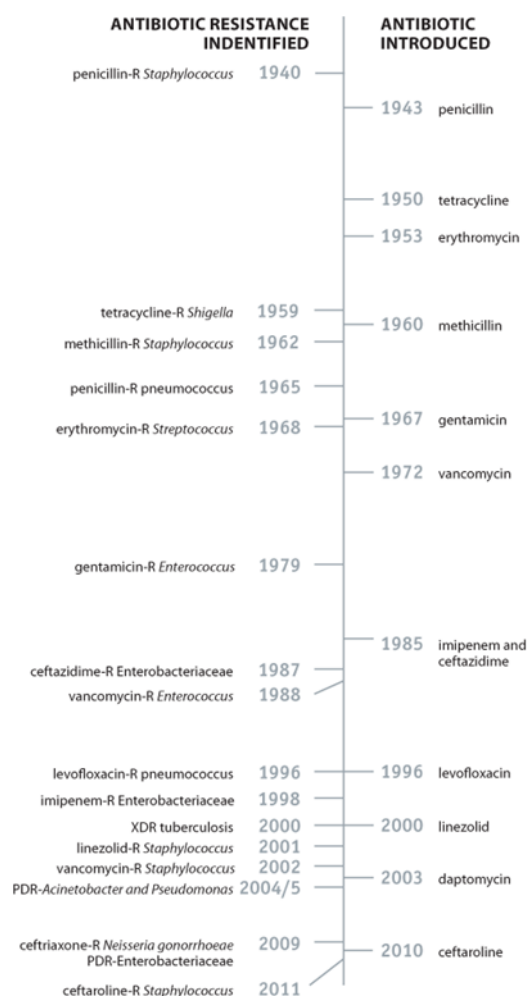
often operate with limited resources, and this lack of resources makes bringing drugs through clinical trials challenging. This is evident when looking at the pipeline of potential antibiotics. Currently, there are only eleven drugs in phase I, thirteen in phase II, and thirteen in phase III clinical trials.²¹

In addition to the small number of antimicrobials in development, discovery of new antibiotic classes has lagged in progress compared to other fields. While there have been several new classes brought to market since 2000, this trend appears inadequate to compensate for the need of innovative treatments [Fig 2].²² Bringing novel antibiotic classes into the drug pipeline is important because resistance to one drug in a certain class often means that those bacteria will be resistant to all other drugs in that class.

Current Policy Proposals from Global Stakeholders

There is considerable global consensus that policies need to change to protect the clinical utility of antimicrobial drugs while also encouraging the development of new ones. Over the past few years, stakeholders in the U.S., E.U., and the WHO have proposed and implemented economic incentives to help drive investment in R&D and to promote stewardship²³. In 2015, the WHO endorsed a Global Action Plan on Antimicrobial Resistance to set objectives for all member states to pursue development and implementation of practical incentives.²⁴ The five objectives are 1) improve awareness and understanding of AMR, 2) use surveillance and research to improve knowledge and evidence, 3) reduce the number of infections through sanitation, hygiene and preventive measures, 4) optimize appropriate use of existing antimicrobials, and 5) advocate for sustainable investment in the development of new medicines, diagnostics, and vaccines to treat microbial infections.²⁵

Figure 2: A history of resistance



Source: <https://www.cdc.gov/drugresistance/about.html>

In the U.S., the White House, bipartisan members of Congress, and regulatory agencies have been engaged in developing ways to spur antimicrobial drug development. In 2014, the White House released the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB), and the subsequent National Action Plan for CARB in 2015, which mirrors the goals set out by WHO and seeks to generate policy action and coordinate resources across key priority areas, including facilitating discovery and development of new, effective drugs and ensuring their optimal use in the health care system.²⁶ Other areas of focus include slowing the emergence of resistance through prevention efforts, strengthening infection surveillance networks, generating diagnostics, and improving international collaboration. Based on these five goals, the Presidential Advisory Council on Combatting Antibiotic-Resistant Bacteria (PACCARB) has established five working groups.

Hospital and Critical Access Hospital (CAH) Changes to Promote Innovation, Flexibility, and Improvement in Patient Care

The Centers for Medicare and Medicaid Services (CMS) recently released a proposed rule, which would require hospitals to develop and maintain an antibiotic stewardship program in order to participate in Medicare and Medicaid.¹ Hospitals would have flexibility in meeting the requirements of stewardship and surveillance by following a set of nationally recognized guidelines of their choosing, including those from SHEA (Society for Healthcare Epidemiology of America) or IDSA (Infectious Disease Society of America). A recent study by the Pew Charitable Trusts found that implementation of Antibiotic Stewardship Plans, designed to minimize overuse or improper use by providers, was effective at reducing inappropriate antibiotic use and improving patient outcomes.²

¹ <https://www.federalregister.gov/documents/2016/06/16/2016-13925/medicare-and-medicaid-programs-hospital-and-critical-access-hospital-cah-changes-to-promote>

² <http://www.pewtrusts.org/~media/assets/2016/04/apathobetterantibioticstewardshipinpatientsettings.pdf>

The goal of facilitating discovery and development of new antimicrobials is an important area, and in 2016 a biopharmaceutical accelerator, termed CARB-X, was launched. CARB-X is a public-private partnership, and partner organizations include four life science accelerators and three research institutes. The focus of CARB-X is preclinical discovery and development, with the goal of cultivating a broad portfolio of antimicrobial products that can be translated into promising candidates in the clinical development pipeline.²⁷

Surveillance is another key element that was discussed broadly by PACCARB, and proposed as a way to build on current CDC efforts including the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) and the National Healthcare Safety Network (NHSN).²⁸ CDC continues to improve and expand these surveillance efforts; in their March report, PACCARB additionally recommended the following critical actions: sustained funding, coordination between the CDC and state prevention programs, and improving adherence by healthcare institutions to report on bacterial isolates.

The Transatlantic Taskforce on Antimicrobial Resistance was created in 2009 as an agreement between the U.S. and the E.U. The taskforce is committed to focusing on three areas: 1) appropriate use of antimicrobials in human and veterinary settings, 2) prevention of healthcare- and community-acquired drug-resistant infections, and 3) strategies for improving the antimicrobial pipeline.²⁹ The agreement also proposed continued collaboration between the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) on sharing information about new incentives for drug manufacturers to invest and develop antibiotics.³⁰

In the U.K., the Review on AMR was commissioned by the U.K. Prime Minister, with support from the Wellcome Trust. Until September 2016, Lord Jim O'Neill was chair of the Review, and the goals of the group included examining the economic issues surrounding antimicrobial development and developing recommendations to improve them. In May 2016, the Review on Antimicrobial Resistance released a report detailing a comprehensive plan aimed at tackling AMR

globally. Their final report specified ten steps that fell into categories of reducing demand, increasing the number of effective antimicrobial drugs on the market, and building a global coalition to address AMR (Table 2). This report estimated that the cost of these efforts would be \$40 billion over 10 years.

In Europe, the Innovative Medicines Initiative (IMI) has established a public-private partnership program called “New Drugs for Bad Bugs” (ND4BB), and part of this organization, COMBACTE, focuses on establishing a clinical trials network for antimicrobials.³¹ Another part of IMI’s ND4BB is DRIVE-AB, a consortium comprised of 23 public and private partners from 12 different countries. The group has been working to define “responsible antibiotic use” with both qualitative and quantitative indicators. Additionally, DRIVE-AB is evaluating the current antibiotic resistance landscape from clinical and economic standpoints across socioeconomic backgrounds, and will continue to work with simulation models to assess the future impact of antibiotic resistance.³² This information will inform models to estimate the value of new antibiotics based on viewpoints from payers, clinicians, and patients and will help create economic strategies to encourage development of new antibiotics and support judicious use of current antibiotics.³³ Leading up to their conference in June 2016, DRIVE-AB released a shortlist of five incentives that could be implemented to increase antimicrobial innovation (Table 3).

In addition to the proposals put forward by these government-sponsored organizations, in January 2016, a group of private stakeholders that includes pharmaceutical, biotechnology, and diagnostics companies, published a declaration of their commitment to combatting antimicrobial resistance.³⁴ The

signatories committed to working to reduce antimicrobial resistance, investing in research and development that addresses public health needs, and improving access to new and effective antimicrobials. Within a few months, 98 companies signed the declaration to reduce drug resistance, increase investment in antimicrobial R&D, and improve access to antimicrobials.

Economic Proposals to Spur Antimicrobial Development

There are two major categories of incentives aimed at supporting the development of critically

Table 2. Actions recommended by the Review on Antimicrobial Resistance

1. Conduct a massive, global public awareness campaign
2. Improve hygiene and prevent spread of infection
3. Reduce unnecessary use of antimicrobials in agriculture and dissemination into environment
4. Improve global surveillance of drug resistance and consumption in humans and animals
5. Promote new, rapid diagnostics
6. Promote development and use of vaccines and other alternatives
7. Improve the numbers, pay, and recognition of people working in infectious disease
8. Establish a Global Innovation Fund for early-stage research
9. Better incentives to promote investment for new drugs and improving existing ones
10. Build a global coalition by leveraging the G20 and UN

Table 3. Shortlist of incentives from DRIVE-AB

Incentive/Model	Type ¹	Type of innovation stimulated	De-linkage ²	Promotes sustainable use	Promotes equitable availability
Grants: Non-repayable research funds	Push	Early phase research	n/a	Untested	Untested
Non-Profit Antibiotic Developer: An independent organization that manages and finances a portfolio of antibiotic discovery and development projects through to commercialization	Push	Incremental innovation and development with a higher risk profile	n/a	Strongly	Strongly
Diagnosis Confirmation Model: A dual-pricing model where a premium price is charged if the antibiotic is used for the entire course or a lesser price if the antibiotic is used first empirically and then promptly deescalated	Pull	Greater diversity of broad and narrow-spectrum antibiotics with significant improvements	No	Moderately	Weakly
Insurance Licenses: An annual license paid to a manufacturer to have access to a specific antibiotic, up to a specified volume	Pull	Rarely used, emergency antibiotics	Yes	Strongly	Weakly
Market Entry Rewards: A series of predefined lump-sum payments awarded to the developer after regulatory approval of an antibiotic meeting predefined characteristics	Pull	Most pressing public health threats	Yes	Strongly	Strongly

¹ Pull = developers are rewarded for specific results; Push = R&D costs are supported

² Delinkage = revenues are not linked to consumption

Source: <http://drive-ab.eu/wp-content/uploads/2016/06/WP2-Prereading-FINAL.pdf>

needed antimicrobials, referred to as “push” and “pull”. Push incentives aim to reduce the initial cost of research and development and therefore lower some barriers to entry. These incentives are awarded early in the lifecycle of a drug and can significantly reduce the investment that needs to be made by the company; however, the risk of failure during this period is higher and incentives shift risk to the funder. Within the U.S., several push incentives have been proposed or are available for antimicrobial developers (Table 4). BARDA has played a large role in providing push incentives for developers during preclinical and clinical development by forming public private-partnerships; most recently, the spin-off, CARB-X, has provided an outlet to accelerate the development of all innovative antimicrobial products.³⁵ For comprehensive support for a robust and sustainable pipeline, pull incentives are also necessary. Pull incentives aim to provide a reward once the product is approved and on the market. When an incentive is awarded late in the lifecycle of a drug, the company has borne the majority of the risk, so the reward for their work must be higher than a reward that is given early in the lifecycle. Conversely, while a push incentive may be better targeted to support early-stage development, they do not necessarily support the development, production, and reliable availability steps needed for effective antimicrobial treatment. Few pull incentives are currently in effect, but several proposals have been gaining attention as a result of a renewed international focus on the problem of AMR. The following sub-sections will focus in more detail on recent proposals for antimicrobial pull incentives.

Table 4. U.S. Push Incentives for Antimicrobials

<i>Initiative</i>	<i>Sponsor organization</i>	<i>Description</i>
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 early clinical testing.
CARB-X	BARDA and NIH	World’s largest public-private partnership; partner organizations include four life science accelerators and three research institutes. This organization will be focused on preclinical discovery and development. The goal of CARB-X is to cultivate a broad portfolio of antimicrobial products that can be translated into promising candidates in the clinical development pipeline.
Tax credits for research and development	Pending House bill, “Reinvigorating Antibiotic and Diagnostic Innovation Act”	Would allow companies to receive tax credits equaling 50% of clinical testing expenses for an infectious disease therapeutic or diagnostic.
Limited population antibacterial drug (LPAD) pathway	Approved House “Antibiotic Development to Advance Patient Treatment” (ADAPT) Act and pending Senate “Promise for Antibiotics and Therapeutics for Health” (PATH) Act	Would allow antibacterial 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.

Volume-based pull incentives

In the U.S., there are many factors that contribute to the amount of return that a drug product receives once it is launched. Drug price, the period of exclusivity, and the size of the market are important factors. Following approval of a drug, the drug manufacturer has a limited amount of time to recoup the investment before potentially facing competition from a similar drug or from generics. This period of time is determined by both patent protection, which is a set period of time granted by the U.S. Patent and Trademark Office, and marketing exclusivity, which is granted by the Food and Drug Administration (FDA) upon approval of a drug. Market exclusivity is a key factor for drug manufacturers

and investors as it provides predictability on the potential return of investment. As a result, a **market exclusivity extension** is a highly valued incentive for drug developers, particularly for drugs with large markets.

In 2012, the U.S. granted additional exclusivity to antimicrobial drug developers in the form of the Generating Antibiotic Incentives Now (GAIN) Act, which designates both fast track and priority review status and increases the market exclusivity period for drugs that target qualifying pathogens. To date, FDA has designated 58 drugs (antifungals and antibacterials) as Qualifying Infectious Disease Products (QIDP) to treat serious infections; of these designations, six antibacterials have already been approved and 47 antibacterials are under development.³⁶ However, the QIDP designation can be applied to most antibacterial products, and extending the market exclusivity of a drug with low market share does not provide large returns.

Building on the GAIN Act, the House has also introduced the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act of 2014 (DISARM Act), which would allow **add-on Medicare payments** to innovative antibacterial drugs as part of a bundled Diagnostic Related Group (DRG) for inpatient care.³⁷ Since the DRGs account for only the average cost of care for a specific disease in a prior period, they do not take into consideration the higher cost of innovative medical products during the initial years after the product has reached the market. Consequently, the Centers for Medicare & Medicaid Services established the **New Technology Add-On Payment (NTAP) program**, which gives companies an added reimbursement incentive for a specific time (e.g. one to three years) after medical products have been marketed.³⁸ However, this incentive has had little impact. To date, only fidaxomicin (DIFICID) has been approved for this program, but it failed to win approval for a two year extension because CMS no longer considered it to be new.³⁹ Another antibiotic, dalbavancin (Dalvance) was denied inclusion in NTAP because it did not meet substantial clinical improvement criteria.⁴⁰

The programs described above rely on volume-based revenues. One other option that would take into account low potential volume would be to price innovative antimicrobials very high. While this strategy may provide better returns, it could also result in undesirable outcomes. Higher prices could discourage doctors from using antimicrobials appropriately, which means that some patients might not be treated with the right drug leading to potentially worse outcomes and increased resistance as any bacteria that can tolerate the drug will survive and potentially pass their resistance to other bacteria.

Further, both exclusivity incentives and higher prices that increase the returns to drug utilization can be at odds with effective stewardship, which involves judicious use of specific antimicrobials to only clinical cases when they are truly needed. Incentives that remove the dependence on sales volume for return on investment are referred to as **de-linkage** models, and have potential to boost innovation while reducing use and maintaining accessibility. As new policy proposals continue to arise, de-linkage is an idea that has much in common with payment reforms being implemented in other areas of health care.

Pull Incentives De-linked from Volume

Development of incentives that de-link reimbursement from sales revenue have the potential to boost innovation, support stewardship, and maintain accessibility by severing or reducing the linkage between drug utilization and payment. In particular, in the case of antimicrobial development, the de-linkage models could provide a significant payment to a manufacturer that is linked to the effectiveness and potentially the availability of an antibiotic when needed, rather than being tied to actual use of a drug. Several groups have proposed de-linkage models, including the Chatham House Report⁴¹, DRIVE-AB⁴², and the Review on Antimicrobial Resistance report.⁴³ These models reward successful development of a drug with a set payment. However, there are many potential ways to finance and implement a de-linkage model, and the most feasible approach is likely to depend on the characteristics of the health

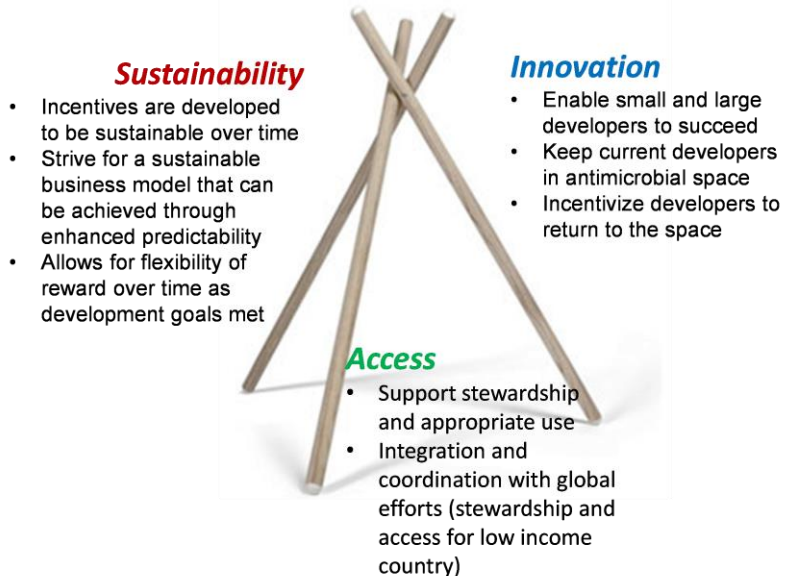
system. For example, a single payer healthcare system might use an existing central government financing entity to adjudicate and make the payments. In a pluralistic system like the U.S., a de-linkage framework that can work across multiple private and public payers may be more feasible.

De-linkage could be achieved by directly providing a lump sum reward or prize when a drug enters the market. These models are called **market entry rewards**, and the **transferrable exclusivity voucher (TEV)** is one example of this model. Extended market exclusivity can be a powerful incentive, though if the antibiotic has limited sales and a relatively low price, the value would be modest. In contrast, if the voucher could be transferred to a non-antibiotic product, it could have a much larger impact on returns on investment in antimicrobial development by allowing extended sales on a much more profitable product. Large companies can use transferable exclusivity vouchers for other drugs in their portfolios, while small and medium size companies, which might not have a very well diversified portfolio, could sell the vouchers or extensions to larger companies for large sums of money, providing funds to recoup the initial investment and potentially continue to invest in new drug development. Because this incentive would not require direct government funding, it would not require the setting aside substantial new appropriations. However, the additional incentive for antibiotic development occurs through raising the cost of treating another group of patients. Extended exclusivity would slow generic entry, delaying access to less costly options.

Another de-linkage model is a **market entry payment**, which provides a cash prize upon approval of an antimicrobial drug with a predetermined amount of money. While the amount of money needed to provide an incentive to developers has been estimated to be between \$900 million and \$4 billion dollars⁴⁴, in 2014, in a report to the Assistant Secretary for Planning and Evaluation, the ERG Group estimated that the expected net present value of an antimicrobial would be \$1.3 billion.⁴⁵ There are several different ways that this reward can be distributed. One is through a **lump sum payment**, which is a large, one-time payment that is paid upon approval. Another way would be through **staggered yearly installments**, which would be smaller, set amounts paid over a set period of time over the life of the patent. These payments should be linked to agreed conditions such as continued availability of the drugs and stewardship practices. While, these models could provide a return on investment in antimicrobials, they might also risk a loss of the drug manufacturer's commitment to remaining engaged in the life cycle of the product. Therefore, a tiered reward structure based on achieving certain benchmarks, like new indications or a different formulation, could be a strategy to incentivize manufacturers to remain engaged.⁴⁶

Core Principles for Antimicrobial Economic Incentives

In consideration of the work done by others and following discussions with a variety of stakeholders, the Duke-Margolis Center for Health Policy has adopted three core principles on which to evaluate potential antimicrobial economic incentives that were initially proposed by DRIVE-AB: **innovation**, **sustainability** and **access**.



Modified from DRIVE-AB slide set (http://drive-ab.eu/wp-content/uploads/2016/06/Roettingen_DRIVE-AB-Conference_2-June.pdf)

Another, related incentive mechanism is a **patent buyout** or **patent licensing**, which would result in a complete or partial government buyout of the drug patent from the company, resulting in transferring ownership in the complete buyout and a licensing deal in the case of a partial buyout. In these models, the company would no longer be able to market the antimicrobial to the public. In a licensing deal, the company could potentially license their drugs to several different governments; however, the governments would have the option of discontinuing the license if resistance develops. In a patent buyout, the purchase would likely need to be made by a consortium of multiple governments to ensure that the funding was sufficient to provide an incentive for the manufacturer. However, developers are generally reluctant to relinquish their patents or intellectual property because they are then unable to generate any additional returns if the incentive that was initially agreed upon is inadequate or is not completed according to the original terms.

A notable drawback of the above publicly-financed models is the relatively large amount of public funds that would need to be paid out by the government once a drug is approved. The appropriation of such large sums seems challenging in the current U.S. political climate. Indeed, these models have encountered financing challenges in other countries with a much higher share of public funding of health care, and proposals have explored alternative financing solutions. The AMR review, for example, suggested a “**pay or play**” model, in which manufacturers would invest in antimicrobial development, or they would be charged a fee.⁴⁷ The AMR review proposal argues that many other therapeutic areas and related therapies (including chemotherapy and surgery) are dependent on antimicrobials, and since the industry as a whole depends on effective antimicrobials, they should all contribute to antimicrobial development by investing in their own antimicrobial R&D or by paying a fee. Another payment model that has been suggested is a tax on all antimicrobial use, including in agricultural applications.⁴⁸

An alternative model to charging fees or taxation is to auction off a set amount of transferable exclusivity vouchers on a yearly basis. The vouchers could have the same terms and conditions as described above, but rather than being awarded to a company upon drug approval, they could be sold to the highest bidder. For example, if the government sold two vouchers worth \$1 billion each annually, then they could expect to raise \$1-1.5 billion per year that could be used to fund a market entry reward. Even though all these models have merit, our analysis of the issues supports the engagement of both the private and public sector in funding development of innovative drugs.

Contract models may be better adapted to implementation of de-linkage in the U.S. because they can be applied to private payers as well as the public payers. The **advanced market commitment** model has been successfully applied to vaccine development, and is potentially applicable to antimicrobial development.⁴⁹ In this model, payers commit to purchasing a certain volume of drug at a certain price. These commitments would create a guaranteed market for the manufacturers. However, uncertainty in actual need and use of the drug (as opposed to vaccines) does not provide an incentive for payers to engage in such model.

Similar to the advanced market commitment model, the **insurance license** model, as considered by DRIVE-AB, requires the payer to pay an annual license fee to a manufacturer for access to a specific volume of antimicrobial. If the volume needed exceeds the predetermined limit, then the manufacturer would be paid an additional amount. A variation of this incentive, the **cap and collar** model would designate a minimum amount of revenue that the manufacturer would receive each year (the collar); however, there would also be a maximum amount (the cap), above which the revenue would be shared between the manufacturer and the payer. While these models could provide predictable returns to the antimicrobial manufacturer and discourage overuse, this particular payment structure has not been used in the U.S. However, it has some de-linkage and value-related features in common with alternative value-based payment models, which we describe next.

Rewarding value in antimicrobial development

As healthcare expenditures continue to rise, U.S. health care reform efforts have focused on value and quality improvement. These broad shifts toward value in health care payment could provide a model for aligning antimicrobial payment reforms. In particular, federal and private payers have begun implementing alternative payment models (APMs), which shift from fee-for-service (FFS) based on volume and intensity of covered services to a reimbursement system based on patient outcomes and overall costs of care. APMs include some payments that are bundled at the level of an episode of care, or at the person-level. These payments enable more flexibility in how services are provided. At the same time, the payments are also tied to better measured outcomes and lower costs, creating more financial accountability for providers that the way in which funds are spent lead to higher-value care.

In early 2016, the Health Care Payment Learning & Action Network (HCP LAN) released a white paper on an Alternative Payment Model (APM) framework that could be applied over time across both private and public health care sectors. The HCP LAN report lays out a path to implementation through four distinct categories. The first represents the current FFS that is typical for antimicrobials and other drugs today. The second category keeps FFS, but adjusts the FFS payments based on quality and value. Some of the FFS-based antimicrobial incentive models, like extra exclusivity periods or add-on payments for high-priority drugs, might be viewed as reflecting this approach. The final two proposed categories move away from the typical FFS model to varying degrees. The third category largely retains FFS payments, but would add in an element of payment that is not tied to volume but rather to population health – for example, a component of payment tied to availability and use of effective treatment of resistant organisms in a population, alongside FFS payments. The fourth category would represent a more complete shift away from FFS payment, with most or all payments based on health results for a population of patients rather than volume⁵⁰; for example, providing a per-member per-month payment to a manufacturer for a drug, with this payment adjusted based on its effectiveness and appropriate use. Given the public health importance of de-linking antimicrobial payments from volume, high-priority antimicrobials could be an important area for developing value-based payment for drugs in the U.S.

As we explore new economic incentives for antimicrobial drugs, we recognize that there are several APMs that could be applicable to antimicrobial payments. **Bundled payments** are a lump sum payment that is used to reimburse a set of services performed by the provider in a specific event/episode. Previous bundled payment experiments have shown evidence in reducing health costs, especially in controlling excess spending in inpatient care. Similar models might be applied to payment for antimicrobials in serious bacterial infections. The average Medicare payment for simple pneumonia increased 7.9 percent between 2012 and 2014, and the per capita spending for urinary tract infections (UTIs) has risen by eight percent in between 2013 and 2014.⁵¹ Bundled payments for specific care episodes could improve treatment efficiency and can be tied to stewardship and use of rapid diagnostics. However, bundled payments do not explicitly provide an incentive for infection prevention.

Another payment model is focused on **population-based** payments through a **per member per month (PMPM)** payment model in which the PMPM amount depends on the effectiveness of the antibiotic and on appropriate use (e.g., measures of stewardship). Both models would allow the manufacturers to have a more predictable revenue stream potentially de-linked to a lesser or greater degree from volume and supportive of stewardship through reduced marketing and pressures to sell. The Duke-Margolis Center is currently working with its **Antimicrobial Payment Reform Advisory Group** [Appendix A] on an approach that would combine the market entry reward concept with a shift to population-based contracts between manufacturers and payers. This approach would provide a sizable reward for companies that successfully market an antimicrobial that meets certain criteria, as well as provide a path to sustainable population-based payments to ensure availability and access to the novel antimicrobial when needed. The proposal will be discussed in the public workshop.

Conclusion and Next Steps

The proposals outlined above represent a wide variety of pull incentive options that attempt to encourage investment and development of antimicrobials that treat our most concerning bacterial infections. If put in place, along with strong push mechanisms that remove some of the financial risk associated with initial development of drug candidates, these measures would make great strides in restoring the pipeline of antimicrobials, which are greatly needed to combat ever-increasing drug resistance. Concerted efforts by stakeholders in the U.S. and across the globe will be needed to truly keep up with AMR's significant threat. Successful implementation of any de-linkage model will require the consideration of several complicating factors, including financial capacity, high-priority areas, access, and maintenance of supply. Future policies should also be focused on promoting development of antimicrobials that treat unmet medical needs while continuing to ensure appropriate use.

External Funding Sources

This work was supported by funding from Merck & Co.

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