INCENTIVIZING NOVEL APPROACHES TO **COMBAT ANTIMICROBIAL RESISTANCE**

TIER ONE PROGRAM "SCIENCE & POLICY" CLASS WHITE PAPER • 2019

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INTRODUCTION

The Global Threat

Antimicrobial resistance (AMR) is the process by which microorganisms, such as viruses and bacteria, develop capabilities that render antimicrobial medicines ineffective in treating infections (World Health Organization, 2019). AMR is a growing concern with an estimated 700,000 people dying from such infections annually (Review on Antimicrobial Resistance, 2016). In a 2013 report, the Centers for Disease Control and Prevention (CDC) estimated that 2 million Americans contract an AMR infection each year, leading to more than 23,000 deaths. The long-term consequences of AMR includes the eventual inability to treat many infectious diseases, leading to more widespread, longer-lasting, and frequently-occurring epidemics (Michael, Dominey-Howes, & Labbate, 2014). Deaths from AMR infections will soon outpace those attributed to cancer, diabetes, and automobile accidents (O'Neill, 2016). Unless new solutions are developed to address this issue, AMR-related deaths will reach 10 million people annually by 2050 (O'Neill, 2016).

The problem of AMR has been growing since the discovery of penicillin, but has grown more prominent in the global health discussion due to resistance to third generation cephalonsporins, multi-drug resistant diseases, and evidence of resistance to last-resort antibiotics (Park, 2014; McGann et al., 2016). Colistin, for example, is typically administered as a last-resort antibiotic for many antibiotic resistant infections (McGann et al., 2016). In 2015, researchers in China identified a transferable Colistin-resistance gene (mcr-1). Shortly after this first documented case, researchers in Belgium identified a second Colistin-resistance gene (mcr-2) (Xavier et al., 2016). Over the past four years, Colistin-resistance genes have continued to spread and current studies show that resistance has been observed on five out of the seven continents. Colistin-resistance has also been observed in both human and animal

populations, suggesting that there are multiple pathways for the resistance to spread, increasing the threat (Schwarz & Johnson, 2016).

Another class of "last-resort" antibiotics is becoming less reliable as the number of multi-drug resistant pathogens grows (Papp-Wallace et al., 2011). Carbapenems are vitally important to treating many different types of resistant bacteria, but resistance to carbapenems has been increasing throughout the world. For example, as recently as March 2019 the CDC expressed concern about carbapenem-resistant Enterobacteriaceae in healthcare settings. Enterobacteriaceae is a family of bacteria which includes E.coli and 50% of people infected with one of these resistant bacteria will die (CDC, 2019).

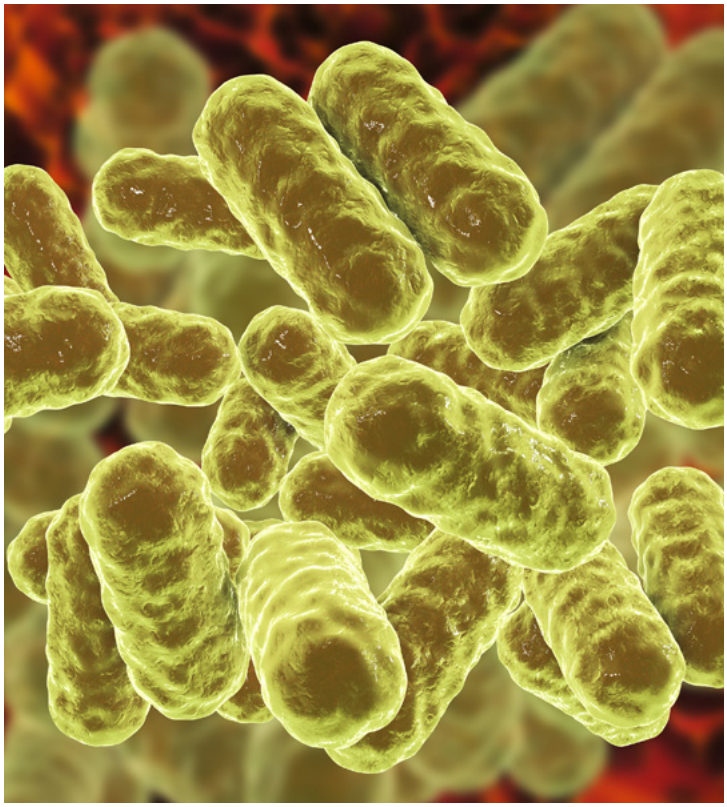
In addition to the development of resistance to last resort antibiotics, one strain of gonorrhea has developed resistance to all antibiotic drugs currently available as treatment (Unemo, 2015). An estimated 78 million people per year are infected with gonorrhea worldwide, 820,000 of which reside in the U.S, meaning that the threat of untreatable gonorrhea is a significant public health problem. The World Health Organization's Global Gonococcal Antimicrobial Surveillance Programme (WHO GASP) monitors the trends of multi-drug resistant gonorrhea across the world and has found that between 2009 and 2014, countries reported resistance to ciprofloxacin, azithromycin, and last-resort extended-spectrum cephalosporins at 97%, 81%, and 66%, respectively. In most countries, the only remaining effective antibiotics for gonorrhea are extended-spectrum cephalosporins and resistance to them has been reported in 50 countries to date (WHO, 2017).

Once harmful microbes develop resistance, their corresponding infections become increasingly difficult to combat. The cost of treating patients with AMR infections has increased two-fold since 2002, for an average national cost of over $2 billion each year (Thorpe, Joski, & Johnston, 2018). In some cases, patients with resistant diseases die from infectious that were previously treatable. AMR has serious repercussions for many medical advancements, such as organ transplants and cancer therapies, which require the use of antibiotics (Centers for Disease Control and Prevention, 2018). If antibiotics are no longer effective in protecting individuals undergoing surgery or chemotherapy, these procedures will become exponentially more dangerous. Resistant forms of some of the most deadly diseases including pneumonia, tuberculosis, malaria, human immunodeficiency virus (HIV), and the flu have also been identified (WHO, 2018).

AMR is a global issue that must be addressed at the local, national, and international levels in order to combat its continued spread. The development of resistance to last-resort antimicrobials across the world demonstrates the importance of developing novel approaches to combat AMR.

Creating Resistance

Microbes develop two types of resistance: intrinsic and acquired. Intrinsic resistance is the result of natural evolution and is expressed by all strains of that species (Davies & Davies, 2010; Munita & Arias, 2016), whereas acquired resistance occurs most commonly through mutations or horizontal gene transfer and is limited to only some strains within a species (Michigan State University, 2011). Acquired resistance is often the result of overuse and misuse of antimicrobials in human and animal health. Mutations are caused by random errors



during bacterial DNA replication or by exposure to mutation-inducing agents, such as antibiotics (Watford & Warrington, 2019). Horizontal gene transfer is the movement of genetic information between microbes allowing AMR genes to transfer directly from one microbe to another. Horizontal gene transfer can occur between live microbes, bacteriophages, or dead microbes. Microbial biofilm is a third mechanism of acquired resistance. A biofilm is a coalition of microorganisms that form a group with a surrounding barrier which protects against antimicrobial substances. The creation and impact of acquired resistance can best be seen in the increase in AMR infections in hospitals and the overuse of antimicrobials in food animal production.

AMR nosocomial infections, or hospital-acquired infections, are quickly becoming one of the most significant challenges for the healthcare industry. A reason that AMR nosocomial infections are on the rise is due to the misuse or overuse of antibiotics in hospital settings, which has been shown to drive resistance (Read & Woods, 2014). The over-prescription of antibiotics is rampant in the U.S. In fact, in some states, the total number of antibiotic prescriptions written annually is greater than the total population of the state (Gross, 2013). Additionally, studies have shown that 30 to 50% of the time, the chosen antibiotic or treatment duration is incorrect and ineffective (Luyt, Bréchot, Trouillet, & Chastre, 2014). Due to overuse and misuse of these drugs, the number of resistant infections has risen and hospitals are frequently forced to rely on the cephalosporin antibiotic class. Increased cephalosporin use has only exacerbated AMR.

Hospitals have become a hot-zone for AMR infections due to the high levels of direct contact between infected patients and staff, which can then spread the AMR microbes to other patients. These microbes can also be spread via contaminated surfaces like beds, door handles, and medical equipment. Nosocomial infections profoundly impact immunocompromised patients. Because immunocompromised patients are most heavily impacted, intensive care units (ICUs) have the highest incidence of AMR infections. Infection rates are approximately three times higher in ICUs than in other parts of hospitals. In fact, the proportion of ICU patients with nosocomial infections is approximately 51% (Fridkin, Welbel, & Weinstein, 1997; Vincent et al., 2009).

Patients with antibiotic-resistant infections are more likely to encounter ineffective treatments, have a slower recovery timeline, experience recurrent infections, and die from their infection. According to WHO studies, AMR infections impact approximately 15% of all patients. In developed countries, 7 out of 100 hospitalized patients will acquire a nosocomial infection and, in developing countries, this number increases to 10 out of 100 patients (Danasekaran, Mani, & Annaduria, 2017). It is estimated that nosocomial infections in the U.S. alone cost 4.5 billion dollars annually, and contribute to 90,000 deaths (CDC, 2004).

Another challenge in the battle against AMR is the use of antimicrobials in food animal production. Of the 32 million pounds of antimicrobials used in the United States annually, half are used non-therapeutically in animals, largely for growth promotion (Landers, Cohen, Wittum, & Larson, 2012). Antibiotic growth promotion is the administration of sub-therapeutic levels of antibiotics, often as a feed component, to enhance the growth of healthy animals. Though the United States has curtailed antibiotic growth promotion in animal

production, it is still practiced in at least 45 countries (World Organization for Animal Health, 2018).

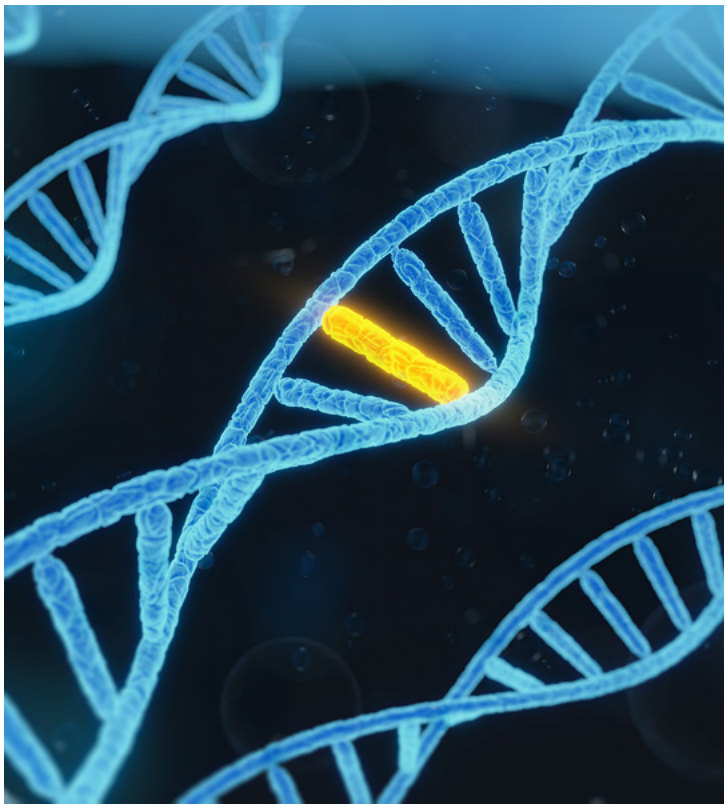
Overuse and misuse of antimicrobials in both humans and food production animals is the primary driver of AMR. We believe it is imperative that novel approaches are developed to address the problem. In the following section, we discuss what is meant by "novel approaches" and expand on the importance of pursuing these innovative measures to overcome the global health challenge of AMR microbes.

Novel Approaches

For this paper, "novel" is an innovation that is currently underemployed or in the process of being developed as a technique or therapy innovation for combating AMR. Though there are many promising, innovative ways to fight AMR infections, incentives to fund such novel therapies and technologies are lacking. In this section, we will discuss several novel approaches that will help combat AMR, given the appropriate incentives are implemented. These innovative methods include AMR outcome studies, genetic algorithms for dosing optimization, combination therapy, and phage therapy.

Clinical studies on the effects of new or altered antimicrobials are generally evaluated on whether they can effectively treat a patient rather than the potential impact they will have in accelerating AMR. Though many antimicrobial studies mention the threat and magnitude of resistance, the assessments of these drugs do not include resistance outcomes. Future FDA approvals should consider the potential for a drug to spur resistance. The addition of AMR outcomes in drug studies and incorporation into the drug approval process will not only enhance clinical results but also support the battle against AMR.

Another potentially novel approach is to determining the most effective antimicrobial drug with the optimal dosage and duration. Finding ideal treatment dose and duration is a difficult task that medical providers face in clinics and hospitals daily. When formulating treatment regimens, doctors must consider numerous factors specific to each patient including age, chronic diseases and comorbidity, immune system strength, inherent genetic makeup, location of infection, severity of infection, and interactions with current medications.



According to Hall, McDonnell, and O'Neill (2018), the majority of antibiotic dosing studies are from the 1960s and 1970s and have been given little attention since, so dosage optimums, intervals, and durations are not based on the current population or special populations with additional health parameters. Conducting studies to optimize dosage provides an excellent opportunity to combat AMR without the invention of new drugs or technology.

Genetic algorithms and combination drug therapies also have potential to limit AMR by prescribing medication regimens that focus on effectively treating the patient and slowing AMR. A genetic algorithm is a computational method based on natural evolution used to determine optimal or near-optimal solutions (McCall, 2005). Genetic algorithms are used in many fields but are increasingly used in medicine for chemotherapy, diagnostics, and treatment regimens for chronic diseases, like atherosclerosis, and acute diseases, like HIV (Ghaheri, Shoar, Naderan, & Hoseini, 2015). Paterson, Hoyle, Ochoa, Baker-Austin, and Taylor (2016) showed that genetic algorithms can be used to determine the minimum dose of a single antibiotic that will successfully eliminate an infection. Simply put, genetic algorithms can

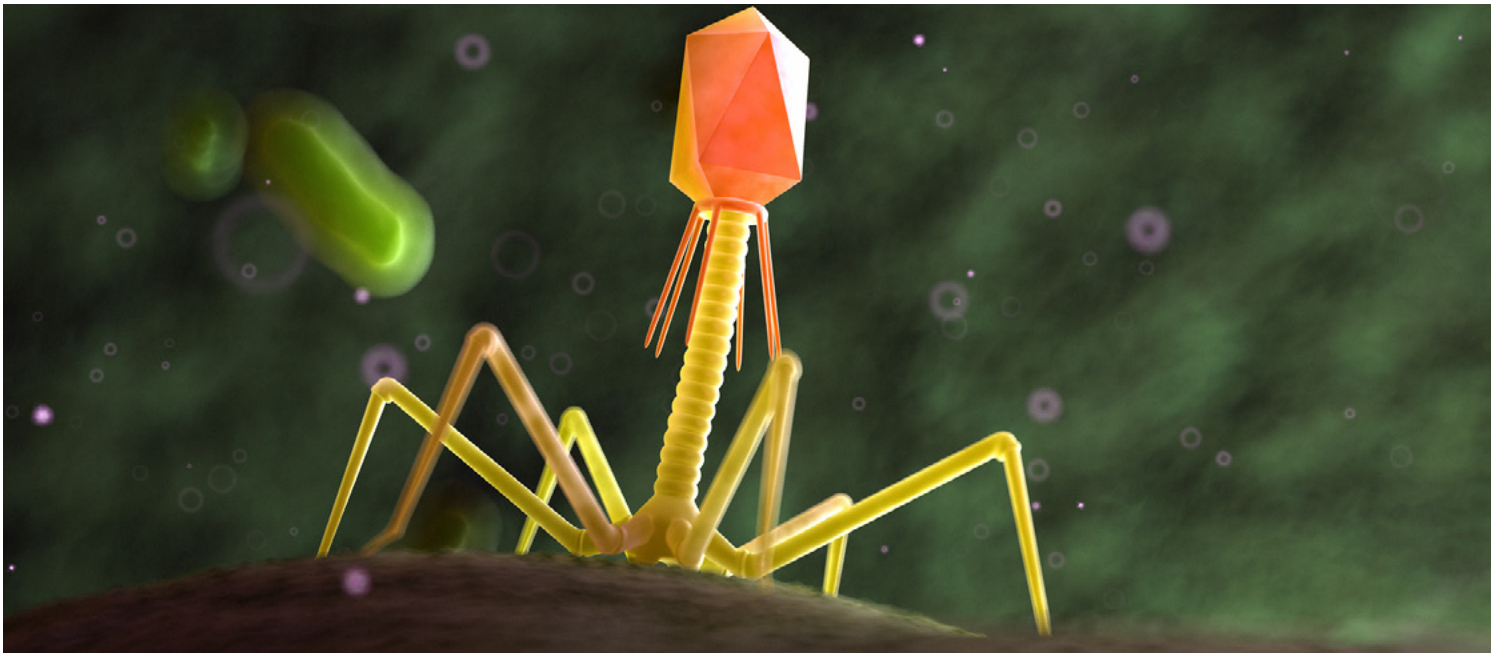
improve drug regimens by minimizing unnecessary use of antimicrobials while still treating an infected patient.

Combination therapy can be an effective way to overcome some AMR challenges. Combination therapy, or polytherapy, is the use of a set of medications, rather than a single medication, to treat an infection. Though subject to the same considerations as a single drug treatment regimen, combination therapy can slow the development of AMR. The reduced risk of developing resistance with combination therapy is due to the varying nature by which resistance can develop. The most successful combination therapies, specifically with regards to preventing AMR, will target the pathogen in multiple, independent, and essential ways. Beyond clinical efficacy, combination therapies for patients with hypertension, prostate enlargement, and Crohn's disease are often more cost-effective than monotherapies - encouragement for developing polytherapies for infectious disease.

Lastly, a promising novel approach is the use of bacteriophages to treat resistant infections. Bacteriophages, or phage, are a class of virus that infect only bacterial organisms. They infect and replicate within a host bacterial cell, killing it in the process (Brüssow & Hendrix, 2002). Many different forms of phage exist, and they are all specific to certain bacteria. Before the development of antibiotics, there was considerable research into bacteriophage therapy as a way to protect human health, but after the advancement in antibiotic drugs, phage technology was pushed aside.

Despite the diminished interest, countries like Russia, Georgia, and Poland continue to use phage for medical purposes (Abedon, Kuhl, Blasdel, & Kutter, 2011). As AMR continues to threaten human health, phage technology is again growing in popularity. This innovative research is creating a new class of antibacterial pharmaceuticals (Lin, Koskella, & Lin, 2017).

Phage technology, in addition to genetic algorithms, combination therapies, optimization of dosage, and AMR impact studies, can all help to combat the global challenge of AMR if adequately supported by both governments and industry. The purpose of this white paper is to promote and incentivize novel innovations, like those discussed above, focused on combating AMR. We start by outlining the challenges inherent in the current development process, including issues with funding, the clinical trial process, and public-private partnership models. We provide an overview of the economic challenges upon entry, including high research and development costs, unpredictable return on investment, and intellectual property challenges. We finish by providing recommendations for areas of improvement.



DISINCENTIVES TO THE DEVELOPMENT OF NOVEL APPROACHES FOR COMBATING AMR

In 2012, Congress recognized the disincentives for drug companies to develop new antimicrobial drugs, such as the costly nature of the research, trial periods, and market uncertainty, and addressed these issues by passing the Food and Drug Administration Safety and Innovation Act. This legislation incentivizes drug companies to continue developing new antibiotics by extending the exclusivity period for qualified infectious disease products by five years. It also afforded the Food and Drug Administration (FDA) with the ability to accelerate the approval process for treatments related to severe, life-threatening diseases, such as AMR (Food and Drug Administration Safety and Innovation Act, 2012).

The 21st Century Cures Act of 2016 sought to address AMR in three critical ways. First, it mandated new responsibilities for the Secretary of the Department of Health and Human Services (HHS) concerning resistance monitoring, including including publishing regular reports on resistance trends and providing assistance to individual states with AMR prevention activities. Second, it created a new review mechanism known as the "Limited Population Pathway for Antibacterial and Antifungal Drugs" that allows the HHS Secretary to approve a new drug meets standards and if it is needed to treat a life-threatening emergency in a limited population. Lastly, the act created the "Susceptibility Test Interpretive Criteria for Microorganisms," a streamlined process that ensures the government, healthcare providers, and patients have access to the most up-to-date information on the susceptibility of infectious organisms (Congressional Research Service, 2016). .

The Pandemic and All-Hazards Preparedness Act (PAHPA) of 2006, while focused on a wide array of measures to combat biological crises, was instrumental in the early fight against AMR. The law's passage led to the creation of the Biomedical Advanced Research and Development Authority (BARDA), an entity that has "worked to form innovative, flexible partnerships and make sound investments in products that can be used to fight the threat of antibiotic resistant bacteria"

(Public Health Emergency, 2017). Currently, BARDA has created a portfolio of fourteen potential antibiotics and two diagnostic tools; within two years, BARDA hopes to move these products out of development and into the marketplace (Public Health Emergency, 2017).

These legislative acts show that there is a political investment in solving the problem of disincentives, but the problem has not yet been overcome. While investing in pharmaceutical development and incentivizing novel technologies to combat AMR is a natural response to the ongoing AMR crisis, some incentives and funding schema have, historically, had a limited or even adverse effect on encouraging pharmaceutical research and development. To select appropriate measures for incentivizing the development of technologies that combat AMR, we must understand how current funding schema is helping or, in some cases, hindering the process. The two primary disincentives are the high costs of research and development and the low-profit expectations for antimicrobials and other technologies that combat AMR, one or both of which must be alleviated to incentivize companies effectively. The next section details the obstacles companies face when undergoing antimicrobial development.

High Costs for Research & Development

The cost of developing a new vaccine or drug therapy for human use can exceed $1 billion and take longer than 12 years to develop and test the new treatment before it is available to consumers (Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria., 2017; Sertkaya et al., 2014; Daniel et al., 2017). Not only is the cost to develop new treatments extremely high, but the low success rate of developing antimicrobial drugs serves as an additional disincentive for pharmaceutical companies to invest in them. On average, from pre-clinical research to FDA approval, the probability of identifying a new molecule, developing a drug, and entering the market is only 6-10% (Sertkaya et al., 2014; Daniel et al., 2017). This low success rate means that the majority of the time companies will invest in a product for which they will see no return. A 2009 study by Vernon, Golec, Lutter, and Nardinelli, however, showed that a 10% decrease in approval times of new drugs by the FDA could lead to an increase in spending on research and development by 1-2%, suggesting that decreased time to market entry could help spur increased development of new products.

One of the primary reasons that the development of a new product is so expensive and time-consuming is because of the required clinical trial process. Chapter V of the Federal Food, Drug, and Cosmetic Act addresses the safety verification process before new drugs and products are approved for commercial use (Federal Food, Drug, and Cosmetic Act. 181, 2018). This Act includes the Kefauver-Harris Amendments, passed in 1962, which require the FDA, for the first time in history, to obtain evidence of proof of efficacy for a drug. This requirement established the phased clinical trials that are now central to the drug approval process (Greene & Podolsky, 2012). While proving the efficacy and safety of a new drug is imperative, this trial process dramatically increased the cost and length of time required to bring a new drug to market.

The current approval process for new drugs or medical devices follows one of two paths: standard or accelerated (Food and Drug Administration, 2018). The standard process includes analyzing the disease or illness that the drug or device is developed to address and current drugs and devices that are already available. Afterward, the benefits and risks of using the new drug

or device are reviewed. The data that support both the benefits and risks are expected to be submitted by the manufacturer after a minimum of two clinical trials have been conducted. This process typically takes about ten months (FDA, 2018). Accelerated approval is designed to fast track the approval process for therapies developed to treat severe, life-threatening conditions. This process allows for FDA approval before the completion of the clinical trial process, but does require the manufacturers to conduct post-marketing clinical trials of the product for verification of risks and benefits.

The FDA has three drug development designations that encourage the development of drugs that could have significant benefits over existing drugs: fast track, breakthrough therapy, and priority review (FDA, 2018). These designations aim to reduce the high costs related to research and development of these drugs—particularly clinical trial costs. Unfortunately, high costs and the lengthy timeline of clinical trials still serve as a deterrent for many companies.

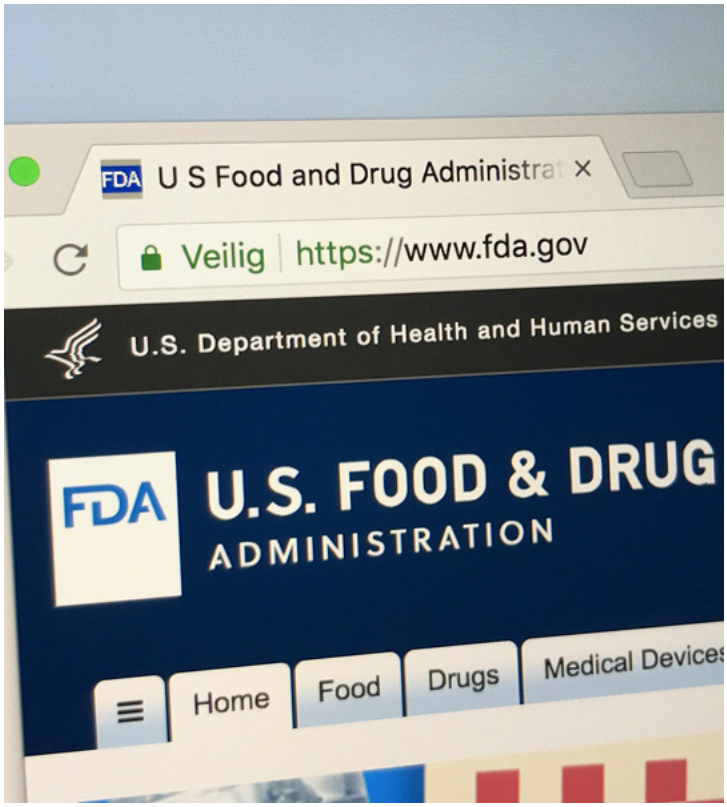
While the costs and timeline of clinical trials are often discussed as a disincentive for the development of new drugs and therapies, the likelihood of failure in the clinical trial stage is another challenge that limits development of new drugs and therapies. Failure in this stage means that the company developing the drug or treatment will likely lose millions of dollars, as well as years of work dedicated to the development of the product. It is difficult to know precisely why clinical trials fail because the information is proprietary, but it is becoming increasingly available due to the Food and Drug Administration Amendments Act of 2007 and the Department of Health and Human Services (HHS) Final Rule for Clinical Trials Registration and Results Information Submission.

To better conceptualize the risk associated with the clinical trial stage, we examined the list of current and recent clinical trials from ClinicalTrials.gov. From this analysis, we determined that roughly 15% of clinical trials that passed the recruitment phase (i.e. the phase were participants are enrolled in the study) were either suspended, terminated, or withdrawn. Of the suspended, terminated and withdrawn studies, 90% of those reviewed were stopped early for reasons other than high levels of efficacy. Some of the studies showed a lack of efficacy or safety concerns (National Institutes of Health, n.d.). Other studies, particularly those funded by pharmaceutical companies, were discontinued as a result of funding reallocation before beginning or completing the study (NIH, n.d.). In other words, the trials were terminated due to a lack of funds.

Developing a new drug or treatment is a difficult, expensive, and time-consuming task. The high failure rates during the clinical trial stage can also serve as a deterrent for companies to even begin development. This is a serious obstacle to combatting the rising threat of AMR, but it is not the only threat. In the next section, we will discuss how low-profit expectations of antimicrobials are continuing to create disincentives for the development of new therapies and demonstrate that the challenges of creating incentives for research and development in this field are complex and multi-faceted.

Low-Profit Expectations

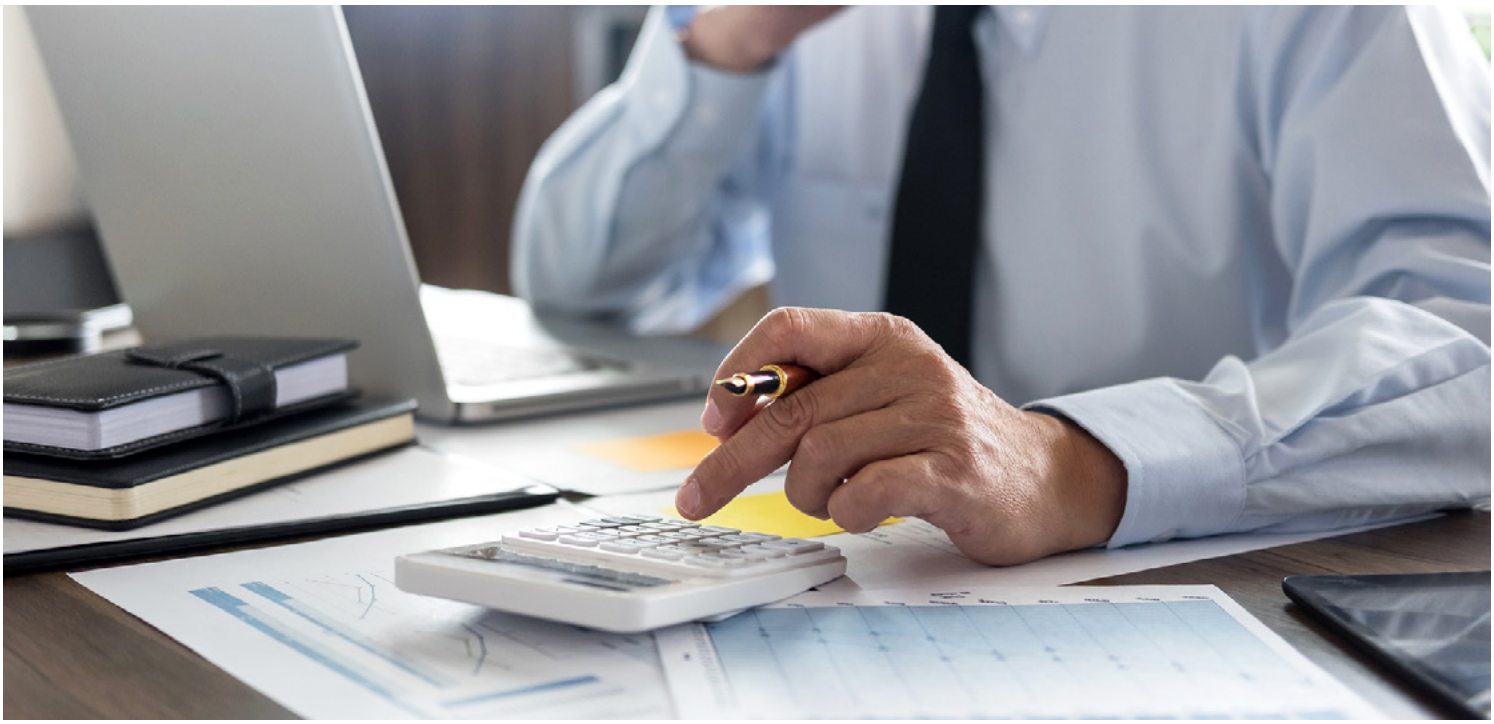
The pharmaceutical industry's investment in antimicrobial research and development has been decreasing for three decades as a result of poor profit expectations relative to other opportunities. In 1990



there were 18 large companies active in antimicrobial research and development. In 2005, this number had dropped to eight (Towse & Sharma, 2011). By 2014, there were only five major pharmaceutical companies that had antibiotics in clinical development (Daniel et al., 2017). The decline in antimicrobial research and development is significantly impacted by the low-profit expectations for antimicrobials in relation to other pharmaceutical products. For example, in recent years, annual sales of patented, brand-name antimicrobials were between $24 million and $75 million. Brand-name oncology drugs have annual sales of roughly $500 million. The low expected profit for antimicrobial development is not attractive when compared to the returns seen for other drugs (Daniel et al., 2017).

This discrepancy in returns can also be illustrated by the expected net present value, or the expected returns over time measured in today's dollars, of antimicrobials versus other pharmaceutical products. Projan (2003) estimates net present value for antibiotics and vaccines to be $100 million and $160 million, respectively, compared to $300 million for oncology, $720 million for neuroscience, and $1.15 billion for musculoskeletal treatments. Another estimate found even lower net present values for six types of antimicrobial drugs, ranging between $4.5 million and $37.4 million (Sertkaya et al., 2014). The low and even negative expected net present value provides a strong disincentive for companies to invest in antimicrobials and vaccines.

Another disincentive related to low-profit expectations is that antimicrobials often have a low expected sales volume. Although approximately 2 million AMR infections occur in the United States each year, the infections are caused by different bacteria, viruses, parasites, and fungi, meaning that the same drug cannot be used to treat all 2 million infections. The dilemma for pharmaceutical companies is that replacement drugs have a relatively small number of potential patients who need it (Daniel et al., 2017). This limited market is exacerbated for drugs that treat pathogens with a propensity for developing resistance because the pathogen will soon develop resistance to the new drug (PACCARB, 2017). The limited and uncertain lifespan of antimicrobials creates a forecasting challenge for companies considering research and development investment (PACCARB, 2017). Therefore, companies cannot only expect a low-profit on the antimicrobials they do produce, but they must also contend with an uncertain product lifecycle.



CREATING INCENTIVES FOR THE DEVELOPMENT OF NOVEL APPROACHES

Numerous incentive schemes have and can be employed to stimulate research and development of novel treatments and technologies to curb AMR. This section examines promising push, pull, and mixed incentive approaches that have or could support research and development for new or underutilized tools to combat AMR.

Push Approaches

Push incentive schemas stimulate research and development by alleviating costs. These types of funding can, theoretically, be applied to both basic and applied research throughout the research and development pipeline. For this paper, we focus specifically on tax incentives and grants, but we will also examine government regulation structures as a type of push approach.

Tax Credits

Tax credits are the most commonly implemented form of tax incentives (Mossialos, Edwards, Berenson, Gemmill-Toyama, & Brogan, 2010). These credits reduce the amount of money a manufacturer owes the government in the form of tax liability, used to offset research and development expenditures. In some cases, tax credits may be fully refundable and potentially higher than the tax owed. The Economic Recovery Act of 1981 offered a 25% tax credit on research and development spending across all industries, the impact of which was that an estimated 1.6% of all research and development expenditures from 1982 – 1985 were a direct result of the tax credit (McCutchen, 1993). Put simply, the credit is attributed to stimulating competition and increasing research intensity (Chit & Grootendorst, 2018).

The tax credit structure, though potentially beneficial in earlier stages of the research and development pipeline, has received criticism because the government may end up paying twice for delivered products: once through the tax credit, and again for the cost of the actual drugs in the case of government purchase. Additionally, tax credits may not adequately incentivize small-to-medium

sized enterprises (SMEs) because those organizations generally do not have a sizable taxable income. To be more attractive to such firms, tax credits should be deferrable or refundable and structured as grants (Mossialos et al., 2010; Clift et al., 2015).

Grants & Direct Funding

Grants and direct funding also stimulate research and development for antimicrobials and can be structured in a number of ways. In the U.S. grants and direct funding most frequently come from the NIH and typically support basic research and clinical development (Simpkin, Renwick, Kelly, & Mossialos, 2017). These incentives may be structured to support any phase of the research and development pipeline in the form of early-stage and mid-stage grants, clinical development grants, or targeted priority grants, for instance. However, early-stage grants, which incentivize basic research, are often received by academic institutions, not necessarily by the developers who face the high costs and rigors of clinical trials.

Further exacerbating this mismatch in funding is the fact that push incentives are unevenly distributed and heavily focused on early-stage development. In response to this imbalance, Simpkin et al. (2017) suggest there is a need for funding later stages of development, such as clinical trials, as evidenced by the dearth of products in Phase II and Phase III clinical trials. We propose employing clinical development grants, which would fund phases II and III of clinical trials, as a means of bolstering late-stage antimicrobial development (Savic & Årdal, 2018).

Another serious concern in direct funding is whether or not the "right" drugs and pathogens are being targeted. In the most recent Pew Charitable Trust report (2019) of antibiotics currently in development, less than 70% of the drugs listed have the potential to suppress a WHO critical or CDC urgent pathogen. Ideally, grants with an objective to fund novel antibiotic therapies would target pathogens on the WHO Priority Pathogen List. In their discussion on grant frameworks for stimulating novel antibiotic research, Savic and Årdal (2018) recommend priority grants, which would be used to target drug-resistant pathogens from the WHO Priority Pathogen List or identified via gap analysis. Such a grant structure would be paid out based on identified milestones and would primarily fund small-to-medium sized enterprises, industry, and non-profit research.

Funding pharmaceutical research, in addition to basic research, at an early stage can garner high rewards, but poses a significant risk that the product may not

ever make it to market. Given the lack of antimicrobials in later stages of development in conjunction with the significant costs of clinical trials, we recommend utilizing clinical trial grants that specifically target priority pathogens.

Regulatory Structure

In order to understand how government regulations can impact companies' spending on research and development investment and innovation, we must evaluate the studies that analyzed the results from such regulation. In the fight to combat AMR, governmental regulations must be an aid that helps companies create novel solutions and products, rather than a disincentive for development.

Beginning with regulatory compliance issues, Hauptman and Roberts (1987) found that inflexible FDA regulations reduced short-term investments of innovation due to compliance uncertainties, especially within new technology products. However, as companies adapted to new regulations, they were able to confidently invest in more novel and innovative products as long as the regulatory regime remained stable. Wrubel, Krimsky, and Anderson (1997) confirmed this delay in investments and the rebound effect, but argued that the rebound to more innovative solutions was not due to companies' adaptations. Instead, they found that it was due to government clarification of existing regulations. By making existing regulations more clear and well-defined companies were not deterred by the uncertainty of development and implementation protocols. Additional studies by Grabowski and Vernon (1977), Grabowski, Vernon, and Thomas (1978), and Thomas (1990) all observed that the market introduction of new drugs was often delayed due to regulatory and compliance uncertainty. In other words, clarity in the regulatory structure is essential to maintaining competition and innovation.

Aside from regulation clarity, there are other ways that the regulatory process can help promote, rather than disincentivize, development of novel approaches to combat AMR. Studies by Eisenberg (2007) and Katz (2007) found by promoting information sharing or decreasing information asymmetry, government regulations can help stimulate innovation as companies could expect increased returns on successful innovative products. Although many companies might be hesitant to share private and confidential information, the regulatory structure can reward companies that work together, so that funding is not spent on overlapping projects within AMR research and development. Examples, such as the Gates Foundation, can be used as a blueprint for what these regulations can accomplish.

Governmental regulations are meant to create an environment of transparency and efficiency for companies that invest in research and development. Unfortunately, in many cases described above, these regulations create uncertainty over compliance and the costs associated with it. As AMR increases and the need for new technologies and drug options increase, regulations need to be crafted in clear language so companies understand the requirements.

Pull Approaches

Unlike push approaches, which focus on affecting costs, pull approaches increase or modify revenues. These approaches are generally more effective than push approaches for bringing a product to market because they reduce market uncertainty. In this section, we

discuss intellectual property extensions and market exclusivity, which are widely accepted incentives that increase pharmaceutical revenue. Furthermore, we highlight the modification of reimbursement structures and advance market commitments as additional promising pull approaches.

Intellectual Property & Market Exclusivity

According to the Pharmaceutical Manufacturers of America (PhRMA), intellectual property is the system of "laws that enable people and organizations to make the investments necessary to develop new technologies and to defend their proprietary inventions or products" (Pharmaceutical Manufacturers of America, n.d.). This definition reveals the emphasis that pharmaceutical companies place on the law to ensure the protection of their product. The current U.S. intellectual property framework for pharmaceuticals is primarily governed by the Federal Food, Drug, and Cosmetic Act, the Bayh-Dole Act of 1980, and the Hatch-Waxman Act of 1984. Depending on the drug, these laws have produced mixed results for both producers and consumers, but in relation to efforts to combat AMR, the current intellectual property framework has been detrimental to the interests of both the drug manufacturers and the general public. Additionally, national security concerns such as economic espionage and intellectual property theft threaten the ingenuity and productivity of American pharmaceutical producers regarding all products, especially those with an already low return on investment, like antimicrobials.

In the early years of healthcare, generic drugs did not pose a threat to drug manufacturers because physicians were not concerned with drug prices and pharmacists were not allowed to provide patients with the choices of a generic drug, instead of the brand name drug, due to anti-substitution laws (Miller, 2002). This dynamic began to change in the late 20th century, however, with the passage of the Bayh-Dole Act of 1980. The Bayh-Dole Act aimed to incentivize private sector research and development with the use of government funding and stipulated that universities or other entities receiving federal funding are allowed to possess the rights and title of new discoveries, provided no "march-in rights" are claimed by the federal government that would

grant the government possession of the research and development (PhRMA, 2018; University of Pittsburgh Innovation Institute, 2019).

Today, estimates show the Bayh-Dole Act has generated more than $591 billion to GDP and has created roughly 4.2 million jobs (Pressman et al., 2017). More importantly, however, studies suggest that the law led to the creation of more than 1,000 start-up companies and more than 750 products from university laboratories (ATUM, n.d.).

Another pivotal piece of legislation in current intellectual property law is the Hatch-Waxman Act of 1984, also known as the Drug Price Competition and Patent Term Restoration Act. This Act sought to balance innovation and affordability in the pharmaceutical market. Before the law was enacted, only 19% of all prescriptions were filled with generics, only 35% of major drugs had generics, and a 3 to 5-year patent waiting period was in effect before generics could come on the market. Today, due in large part to the Hatch-Waxman Act, nearly 90% of all drugs are filled with generics, more than 80% of pharmaceuticals have generics available, and generics can enter the market immediately after the expiration of a patent (PhRMA, 2018).

Studies also assert that the Hatch-Waxman Act has been successful in lowering prices for consumers and incentivizing both new drugs and generics (Boehm, Yao, Han, & Zheng, 2013). Despite these advances, the cost of developing the original drug was still holding back innovation. To address this, the Federal Food, Drug, and Cosmetic Act was amended in 2012 to extend the exclusive period an additional five years for qualified infectious disease products, such as those addressing AMR (Food and Drug Administration Safety and Innovation Act, 2012). This additional extension protects the drug manufacturer's return on investment which should in return incentivize innovation for novel treatment addressing resistant infections.

Despite the progress that has been made in both stimulating research and development and lowering the price to consumers, consumer advocates do not believe the current system is working for the benefit of all. Pay-to-delay schemes, whereby a pharmaceutical company pays off competitors to prevent the introduction of a generic, have drawn the ire of consumers and the federal

government. The Federal Trade Commission estimates such schemes cost consumers $3.5 billion in higher drug prices every year (Federal Trade Commission, 2019). In January of 2019, Senators Amy Klobuchar of Minnesota and Chuck Grassley of Iowa introduced Senate Bill 64, "Preserve Access to Affordable Generics and Biosimilars Act," to prohibit this practice (S. 64- Preserve Access to Affordable Generics and Biosimilars Act.s, 2019). However, similar legislation has been introduced in previous legislative sessions with no success.

Legislation like Senate Bill 64, while attempting to advocate for the consumer, does not address the core problem and may even lead to unintended consequences. Because antibiotics provide revenue for the producer over an extended period of time, paying off generic producers is a tactic meant to help producers gain what they see as their rightful earnings; if outlawed, pharmaceutical companies may have less incentive to research and develop new drugs—especially those to combat AMR.

With respect to AMR, the current patent and intellectual property framework is not conducive to the development of new antimicrobials. In Superbugs: An Arms Race

Against Bacteria (2018), Hall, McDonnell, and O'Neill argue that the 20-year patent term is, in reality, only a ten-year window after successful testing and clinical trials—leaving a short window for manufacturers to recuperate costs. In contrast to critics who believe the patent system unfairly benefits drug manufacturers, the authors argue that the patent system actually discourages the creation of new antimicrobials.

Intellectual Property Extensions

Intellectual property extensions are a recognized incentive valued by pharmaceutical developers, but it is essential to evaluate the efficacy of their structure, particularly within the context of antimicrobial research. Tradeable vouchers are forms of intellectual property extensions in which the FDA rewards companies conducting relevant antibiotic innovation with transferable vouchers that extend market exclusivity of an existing drug. In other words, the vouchers are not used to protect the market for specific antibiotics, but can be used or sold by companies conducting antibiotic research for oncology drugs, for example. While this mechanism is attractive due to its intangible up-front cost, studies indicate that vouchers and other forms of market exclusivity cost far more to the U.S. healthcare system than they stimulate in research and development spending (Sciaretta, Røttingen, Opalska, Van Hengel, & Larsen, 2016).

The significant cost to consumers associated with market exclusivity are a result of preventing generic drugs from entering the market. Patients and insurance (Medicare/Medicaid, private insurers) will pay significantly more for the protected drug. In fact, some studies estimate that patients could pay as much as 80% more for a drug without competitors in the market (Outterson & McDonnell, 2016), resulting in treatment costs that are prohibitive and may limit patient access. Outterson and McDonnell (2016) estimate that while a single 12-month voucher could stimulate $800 million in research and development spending, the cost to the U.S. healthcare system would be just short of $5 billion. In other words, while tradeable vouchers may stimulate research and development spending, they place an unmanageable financial burden on the healthcare system.

Intellectual property extensions for antibiotics and drugs to combat AMR are only meaningful if the drugs are priced high enough to mitigate costs (Chit & Grootendorst, 2018). Qian (2007) concludes that at a certain point, intellectual property extensions may actually decrease research and development in higher-income countries. Perhaps the most alarming aspect of market exclusivity is that, when applied to antibiotics, it could ultimately result in greater use of the drugs we are trying to protect. In the Chatham House Report (Clift et al., 2015) on antibiotic revenues, the authors state that market exclusivity risks over-marketing the relevant drugs. In other words, market exclusivity could potentially contribute to AMR (Sciaretta et al., 2016).

Intellectual property extensions are an incentive on which the pharmaceutical industry has come to rely, but studies suggest that current implementations of market exclusivity come at a high cost and have limited efficacy. We recommend re-evaluating intellectual property extensions to identify the appropriate extension timeline and structure that will rectify these financial challenges.

Homeland Security, Geopolitics & Intellectual Property Theft

Intellectual property theft by malicious foreign actors is threatening to undermine the entire intellectual property framework and dampen incentives for private research and development. As cyber capabilities continue to develop at an unimaginable pace, both individuals and state actors are increasingly capable of causing harm to private industry, ranging from the loss of revenue or the theft of various forms of intellectual property. The National Cyber Strategy, released in September 2018, describes the current crisis facing the United States:

> *Our competitors and adversaries…benefit from the open Internet, while constricting and controlling their own people's access to it, and actively undermine the principles of an open Internet in international forums. They hide behind notions of sovereignty while recklessly violating the laws of other states by engaging in pernicious economic espionage and malicious cyber activities, causing significant economic disruption and harm to individuals, commercial and non-commercial interests, and governments across the world. (White House, 2018, pg. 1)*

This document names China as the primary party responsible for American intellectual property theft, noting the country is actively trying to steal trillions of dollars worth of American intellectual property (White House, 2018).

Additionally, the National Counterintelligence and Security Center's Foreign Economic Espionage Report of 2018 lists new drugs and vaccines, biopharmaceuticals, and other forms of medical technology as areas of highest espionage interest for malicious foreign actors. The report highlights the international laws that allow for foreign espionage and intellectual property theft. For instance, China instituted a law in 2017 that affects U.S. firms operating in China in a number of ways. The law limits the sale of foreign information and communication technology (ICT) and mandates that foreign companies submit ICT for government-administered national security reviews. It also states that foreign entities conducting business or research in China must store

their data in China, and any attempt to move data outside of the country requires governmental approval (National Counterintelligence and Security Center, 2018). In other words, foreign actors are bypassing U.S. intellectual patent law in various ways at the expense of both American producers and consumers. These actions pose a significant risk for U.S. corporations seeking to develop technologies inside these countries.

The risk of intellectual property theft only compounds the problems that exist in the development of antimicrobials. The possibility of intellectual property theft in the realm of antimicrobials means that companies might expect an even lower return on investment than they ordinarily would. Given the typical return is not high enough to incentivize most companies, potential intellectual property theft may deter a higher number of companies. Recommendations made in the National Cyber Strategy of 2018, particularly the strengthening of international legal cooperation and investments in critical cyber infrastructure, can significantly strengthen the Healthcare and Public Health Sector. Additionally, exploring the creation of a government-sponsored intellectual property theft insurance program for pharmaceutical companies developing critical drugs and technologies could potentially lessen the risks these firms assume when operating against new threats in today's world.

Modified Reimbursement Schema

Modified reimbursement structures, an important means of incentivizing development, can be implemented in multiple ways, such as lump-sum payments, payments based on milestones, and revised pricing schema. One particularly compelling approach to reimbursement is to delink revenues from volume sales, meaning the return on a product is not tied to its sales. Antimicrobials have a highly uncertain market size, and a delinked pull approach could alleviate the corresponding uncertainty in revenue that stems from unreliable sales quantities. Most importantly, relieving manufacturers of the pressure to increase sales can potentially improve sustainability and good stewardship. In fact, many pull incentives stipulate that developers employ good stewardship practices for their payout.

One widely-discussed implementation of a delinked incentive is delinked market entry rewards. Market entry rewards are a series of cash sums, likely beginning with regulatory approval and received at various milestones, that form the developers' revenue for the identified drug. Delinked market entry rewards define, in advance, a drug price that is valid up to a specific sales quantity (Årdal, Røttingen, Opalska, Hengel, & Larsen, 2017). This pricing enables patient accessibility while allowing developers to be reimbursed at a level that is proportionate with the value of the product. The greatest strength of market entry rewards is that they can be tightly coupled with good stewardship through restrictions on the marketing of the drug. To receive the payments, developers must meet stringent contract stipulations, which should be written to dictate limited (or possibly no) advertisement of the drug. This restriction on marketing efforts will ideally stymie overuse of the novel therapy and thus limit potential AMR.

The main disadvantage of entirely delinked market entry rewards is two-fold. First, determining the magnitude of the rewards that will incentivize developers without wasting money is difficult. Second, market entry rewards require significant long-term cash flow. One report estimates that, in order to be financially attractive to

developers, the rewards should add up to somewhere between $800 million and $1.3 billion (Wellcome Trust & UK Government, 2016). With such a sustained and significant payout, this highly effective incentive structure should be reserved for developers who are targeting urgent pathogens (DRIVE-AB, 2016).

Advance Market Commitments

Advance Market Commitments for vaccines are outlined extensively in the Center for Global Development's report: Making Markets for Vaccines: Ideas to Actions (Levine, Kremer, & Albright, 2005). The Advance Market Commitment secures a market for developers by guaranteeing a sales price for some novel drug up to some quantity. The price consumers pay may fall well below this sales price, and sponsors will continue subsidizing the difference between the guaranteed advance market price and the price consumers pay until the pre-defined sales quantity is realized. Developers must agree to continue producing the drug at an accessible price for any sales beyond the initial quantity, and donors are not committed to any further subsidies. Unlike other pull incentives, the Advance Market Commitment is not meant to be a prize, but instead create a market in which multiple developers compete by securing an estimated market size of $3 billion (Levine et al., 2005). The drugs supported by Advance Market Commitments must meet stringent technical specifications. This particular incentive is relatively low-risk to donors, as an expense is only incurred if the drugs are successfully developed and sold.

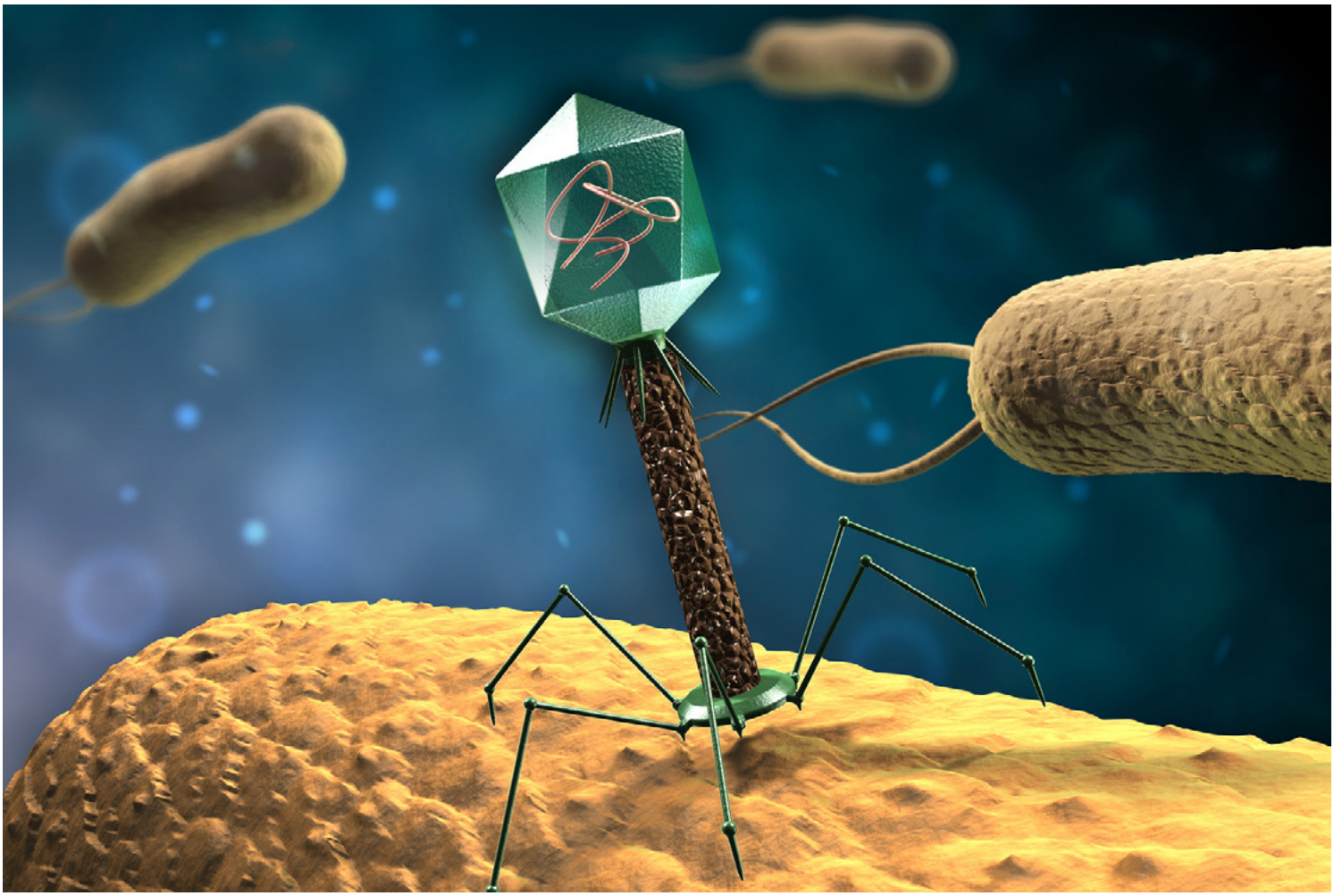
Mixed Incentive Approaches

The Options Market for Antibiotics (OMA) model, proposed by Brogan and Mossialos in 2013, is a mixture of push and pull incentivization based on the ideas

behind Advance Market Commitments and the Call Options for Vaccines (COV) method. COV are similar to call options for stocks; investors will purchase the right to buy some quantity of drugs at a discounted price, assuming the drugs make it to market. In the OMA approach, an investor (such as an NGO or government agency) purchases options to buy the drug at a discounted price when it is market-ready. This investment can be made at any point in the product development cycle, though cost will increase (and risk of failure will decrease) the later the investment is made. In other words, a developer purchasing options earlier in the cycle will face a greater risk but will also enjoy a steeper discount if and when the drug makes it to market (Brogan & Mossialos, 2013).

A second mixed incentive approach is establishing public-private partnerships. Public-private partnerships allow entities such as universities, NGOs, and private corporations to share risk and combine strengths. In general, the two most commonly employed public-private partnerships structures are Product Development public-private partnerships and Precompetitive public-private partnerships. Product development public-private partnerships tend to produce pharmaceutical solutions in an attempt to spur growth in developing countries, while Precompetitive public-private partnerships strive to produce specific scientific innovations. More recently, there has been a push by the scientific community to evaluate existing public-private partnerships structures and more objectively determine their economic and social contributions.

The success of public-private partnerships in the pharmaceutical domain suggest that they might provide a unique solution to the challenges of developing innovative AMR-combating products. For example, in 2003, the Structural Genomics Consortium (SGC) was created, composed of six academic institutions and nine global pharmaceutical corporations. This Consortium was remarkably successful, creating over 1,000 new protein structures, producing over 400 publications, and sharing its findings at over 250 research conferences by 2013. The Consortium was valued at approximately $44 million. This type of innovative collaboration could help overcome obstacles to the development of novel approaches to combating AMR.



CONCLUSION

Resistance to existing drugs is increasing at an alarming rate, and without swift action, we will have no tools to combat future infections with once easily treatable disease. This combination makes AMR one of the most critical challenges in public health and global health security. Infectious disease experts and world leaders agree that the world is ill-prepared to handle a threat that may be inevitable.

Government action to finance and stimulate technological innovation is not unprecedented. As a result of the Advanced Technology Vehicles Manufacturing loan program sponsored by the Department of Energy, organizations like Tesla, Ford, and Nissan have received financing for fuel-efficient automotive development. The ARPANET, precursor to the internet was developed by the Department of Defense Advanced Research Projects Agency (DARPA). Government financing and public-private partnerships are crucial to burgeoning research and development. The risk of widespread AMR is one that is too great to ignore.

This White Paper has documented the many challenges faced by government, industry, and non-governmental organizations (NGOs) in incentivizing the development of new drugs, vaccines, and novel innovations to combat AMR. Our recommendations attempt to address these significant challenges in order to invigorate antimicrobial development and protect and prepare the United States and the world to combat the growing threat of AMR.

RECOMMENDATIONS

1. Provide priority grants for clinical trials.

Developing new therapies to combat AMR is extremely expensive with little return on investment for both academic institutions and pharmaceutical companies. While the clinical trial process is imperative to the safety and efficacy of these therapies, the high costs and lengthy trials, particularly in Phase II and Phase III, mean that many drugs will never make it to market. Providing grants to pharmaceutical companies that are developing new therapies to combat AMR, similar to BARDA's public-private partnership funding structure, could help offset this significant financial burden and stimulate research for much-needed novel antimicrobials.

2. Make government regulations clear and concise.

Government regulations provide either clarity or uncertainty. Therefore, rules and regulations should be crafted to clearly detail what is expected. An important historical example of the impact of unclear regulations is the Medical Device Amendment of 1976 where the reclassification of medical devices resulted in uncertainty and confusion. This led the Government Accountability Office to recommend modifying several provisions of the law (GAO, 1983). Limiting uncertainty surrounding government expectations is one more step in providing a reliable timeline for companies to develop new life-saving drugs.

3. Reevaluate intellectual property extension programs.

There are conflicting objectives between drug companies aiming to maximize profits and patients seeking medications at the lowest prices possible. This conflict complicates the evaluation of intellectual property protections, indicating a need to better understand market mechanisms associated with intellectual property extensions for pharmaceuticals. Modification of intellectual property extensions for drugs should focus on designing policies that mitigate adverse

market effects while maintaining the profitability of drug developers. Two pieces of current legislation seeking to review invalid patents and provide greater openness to the drug patent process, H.R. 1520 (Purple Book Continuity Act of 2019) and H.R. 1503 (Orange Book Transparency Act of 2019), should be debated and considered in Congress.

4. Advocate for the implementation of recommendations made in the National Cyber Strategy of 2018.

Today's globalized world presents new challenges for private industry, especially in the protection of data and proprietary information. The National Cyber Strategy of 2018, the first developed cyber strategy since 2003, makes a number of recommendations that should be implemented with urgency. These proposals, especially the strengthening of international legal conventions and investments in critical infrastructure, can lessen the risks pharmaceutical companies take on when seeking to develop new drugs and technologies.

5. Invest in delinked market entry rewards for critical new therapies.

This pull incentive provides a series of cash sums to pharmaceutical companies after the approval of a new therapeutic, ensuring a revenue stream that is delinked from sales volume. These rewards ensure good stewardship by eliminating the need for mass marketing and potential misuse.

6. Encourage public-private partnerships.

Public-private partnerships allow entities such as universities, non-governmental organizations, and private corporations to share risk and combine strengths. The success of public-private partnerships in the pharmaceutical domain suggests that this type of innovative collaboration could help overcome obstacles to the development of novel approaches to combating AMR.

7. Promote advanced market commitments to promote novel therapies.

Through advanced market commitments, sponsors subsidize per-unit prices of qualifying drugs up to some predetermined sales quantity. This incentive allows consumers to purchase drugs at an accessible price but guarantees a financial return (the sum of the sales price and subsidy) that would make production viable, if the drug proved effective. No expense is incurred by the sponsor if the drug does not make it to market or is not sold.

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Rachel Paige Casey is a starting PhD student in Agricultural Economics at Texas A&M University. She earned her BSE in Kinesiology and MS in Agricultural Economics from the University of Arkansas. She recently completed a Master of International Affairs in International Development and Economic Policy from the Bush School at Texas A&M. Since 2016, Rachel Paige has been the editorial assistant for the *Journal of Drug Education: Substance Abuse Research and Prevention*. Additionally, she has been involved in various research activities regarding the economic, public health, and sociopolitical impacts of infectious diseases as well as the relationship between infectious diseases and conflict.

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Katy Jo Nickelson obtained a BS and a MS in Animal Science in 2016 and 2018 from Texas A&M University. Her studies focused on food safety, microbiology, and meat science. Katy Jo also completed a graduate Certificate in Advanced International Affairs in 2018 at the Bush School. During her master's program, Katy Jo worked as a teaching and research assistant for the animal science department, which allowed her to participate in various research projects, including one through a USDA-funded grant program. She also serves on the board of directors for the MSC Student Conference on National Affairs (SCONA), where she is currently the US Army War College liaison. After graduation, Katy Jo aims for a career in biodefense and biosecurity.

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Thomas Snavely is a graduate student at Texas A&M University pursuing a PhD in Biochemistry with a focus on novel treatments for human infectious diseases. As a part of large international collaborations, his

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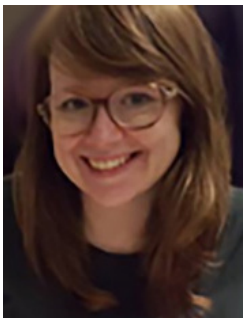
Brittany Segundo



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About "Science & Policy"

"Science & Policy" is a class funded through the Tier One Program by the Office of the President at Texas A&M University. It's an interdisciplinary graduate level course designed to bring together Masters and PhD students from the social sciences and sciences from across the university. Students are challenged to work together over the course of the semester on a research topic within the scope of the course. In Spring 2019, the topic was Antimicrobial Resistance (AMR).

President George H.W. Bush & Lt. Gen. Brent Scowcroft

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