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ANALYSIS OF MARKET CHALLENGES FOR ANTIMICROBIAL DRUG DEVELOPMENT IN THE UNITED STATES

FINAL

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DISCLAIMER

LIST OF ACRONYMS

AM	Antimicrobial
AMC	Advance Market Commitment
AMR	Antimicrobial Resistance
ASPE	HHS Office of the Assistant Secretary for Planning and Evaluation
ASPR	HHS Administration for Strategic Preparedness and Response
BARDA	HHS Biomedical Advanced Research and Development Authority
BSI	Bloodstream infection
CARB-X	Combating Antibiotic Resistant Bacteria
CBER	FDA's Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	FDA's Center for Drug Evaluation and Research
CMS	Centers for Medicare and Medicaid Services
CPC	Cooperative Patent Classification
CRE	Carbapenem-resistant *Enterobacterales*
CRKP	Carbapenem-resistant *K. pneumoniae*
CRO	Clinical Research Organization
CTN	Clinical Trial Network
DRG	Diagnosis-related group
ECRAID	European Clinical Research Alliance on Infectious Diseases
ERG	Eastern Research Group, Inc.
ESBL	Extended-spectrum beta-lactamase
FDA	U.S. Food and Drug Administration
GARDP	Global Antibiotic Research and Development Partnership
GDP	Gross Domestic Product
HAI	Healthcare-acquired Infection
HHS	U.S. Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HTA	Health technology assessment
ICU	Intensive Care Unit
IND	Investigational New Drug
IPPS	Inpatient Prospective Payment System
IQR	Inter-quartile Range
IV	Intravenous
MDRO	Multi-drug Resistant Organism
MER	Market Entry Reward
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NASEM	National Academies of Sciences, Engineering, and Medicine
NDA	New Drug Application
NHS	National Health Service
NICE	U.K. National Institute for Health and Care Excellence
NIH	National Institutes of Health
NPO	Non-profit Organization
NTAP	New Technology Add-on Payments
PASTEUR	Pioneering Antimicrobial Subscriptions to End Upsurging Resistance
PDP	Product development partnership
PPP	Public private partnership

R&D	Research and development
QIDP	Qualified infectious disease product
SARS	Severe Acute Respiratory Syndrome
SLI	Second-line
SME	Small- and Medium-sized Enterprise
TB	Tuberculosis
TPP	Target Product Profile
VRE	Vancomycin-resistant *enterococci*
WHO	World Health Organization
XDR	Extensively Drug Resistant

EXECUTIVE SUMMARY

The market for antimicrobial (AM) drugs is unique in that it is associated with a positive externality (public health)[1] as well as a negative externality (antimicrobial resistance, or AMR) (Mossialos, et al., 2010). AMR occurs when microbes change over time and no longer respond to available medicine. There are several strategies for combatting AMR, including infection control and prevention, stewardship, development of new drug targets and novel treatment approaches, improving diagnostics, developing vaccines, and development of novel AM drugs. Development of novel AM drugs is especially urgent because there are only a limited number of new AM drugs that can treat the multi-drug resistant organisms (MDROs) listed on the WHO priority list (Dall, 2021). Most new AM drugs, however, are not novel, but primarily derivatives of existing AM drugs (Blaskovich, et al., 2017). In addition, AM manufacturers face numerous challenges that have resulted in 15 out of the 18 largest global pharmaceutical companies exiting AM research and development over the last 30 years (Dutescu & Hillier, 2021).

In this report, we examine the scientific, economic, and regulatory challenges in the U.S. market that have impeded the development of novel AM drugs. Our focus is on understanding the market challenges for development of drugs that treat MDRO infections that occur in hospitals in the U.S. and are reimbursed primarily through the diagnosis-related group (DRG) system. We also investigate possible interventions to address the market challenges identified. The objective of this work is to identify new approaches to encourage development of novel AM drugs that could be explored further.

ES.1 METHODOLOGY

To improve understanding of the magnitude of the problem of AMR, we began our study with a scoping review of the literature published in the last 10 years to identify studies that quantify the externality posed by AMR in the U.S. drug market. We also reviewed recent literature on the scientific, economic, and regulatory challenges encountered in the AM drug market in the U.S. We supplemented this literature review with findings from an earlier study in 2018 for which we had conducted a series of semi-structured interviews with AM experts, including early stage developers, venture capitalists, doctors, and hospital representatives, to examine: (1) how drug companies and investors decide to invest in developing new AM drugs; (2) how health care providers determine the value of AM drugs and decide to prescribe them; and (3) what the barriers are to increased investment in AM drugs.

We also examined whether there has been a slowdown in the intensity of early stage AM drug discovery by looking at the number of AM drug compound patents filed and/or granted annually over the last 30 years using Espacenet's searchable patent database. While patents are only one measure of interest in AM drug development and innovation, if AM drug patents are trending downward when patents for all other drugs are trending up, this could point to an allocation of development interest and resources away from AM drugs. To examine this potential market challenge, we compared trends in early stage AM drug discovery to trends in the non-AM biopharmaceutical market as a whole (i.e., all drugs, except for AM drugs grouped together) to evaluate: (1) if there is a slowdown in early-stage AM drug research and (2) if any slowdown is specific to AM drug research or more systemic across the industry.

Additionally, we conducted another series of semi-structured interviews with experts from different organizations to explore inefficiencies in the AM drug market that were not addressed during our previous research, as well as possible strategies for alleviating these inefficiencies (see

[1] All infectious disease drugs, not just AM drugs, have positive externalities because their use reduces the chance of transmitting the disease to others.

Appendix A for our interview questions). Interviewees' organizations included universities, biopharmaceutical companies, foundations, payers/health technology assessment (HTA) groups, and others.

ES.2 SUMMARY OF SCOPING LITERATURE REVIEW FINDINGS

Our scoping review of studies that quantify the AMR externality in the U.S. indicate that the cost of AMR can be very high, although estimates vary widely (Naylor, et al., 2018; Johnson, et al., 2019; Thorpe, et al., 2018). The wide range in estimates is due to definitional differences in the studies, which make it difficult to quantify the problem accurately. Nonetheless, the potential magnitude of the problem is significant. It is therefore important to explore the challenges that impede AM drug development as well as possible interventions to address these challenges. These interventions could, in turn, reduce the AMR externality. While the difficulties encountered in the AM drug market are often characterized in the literature as a market failure, we argue that these difficulties are better characterized as market challenges because drug markets are not perfectly competitive markets and are all inherently subject to market failure.

According to Spellberg (2014), the challenges faced by the AM drug markets can be grouped into three major categories – scientific, economic, and regulatory. Some of the challenges can be classified in multiple categories (e.g., research and development challenges can be viewed as both scientific as well as economic challenges). Our literature review and 2018 study indicated that the major scientific challenges facing the AM drug development market in the U.S. include the difficult science of AM drug discovery, the lack of available diagnostic testing, and the length and expense of research and development. Economic challenges include, in addition to the costs of research and development, the lower return from AM drugs compared to other drugs due to the interrelated factors of low sales volume, lower rates of drug resistant infections in the U.S. (causing lower demand), and the current valuation of AM drugs by society. These economic challenges have resulted in numerous large companies shutting down their AM research in recent years, including Bristol-Myers Squibb, Novartis, AstraZeneca, Sanofi, and Allergan (Megget, 2018). The abandonment of AM drug development by these large companies may drive away further investment. Over 95 percent of the drugs in development today are being developed by small companies, and 70 percent of these companies are pre-revenue, which means they have no products on the market yet that they have developed and commercialized (Pew Trusts, 2021). Regulatory challenges include clinical trial requirements and reimbursement challenges associated with Medicare policies.

ES.3 TRENDS IN AM DRUG DISCOVERY

While the AM drug market in the U.S. faces numerous challenges, AM drug compound patent data show that 2017 has been an inflection point in early drug discovery across the board with significant increases in the number of patents published per year for 2017 and onward. Further, the AM drug compound discovery trend broadly mirrors that of non-AM drug target compounds. Since 2010, there has been around a two-fold increase in the total number of AM and non-AM drug compound patents published worldwide, suggesting that the rates of discovery for new AM and non-AM drug compounds are similar overall. While patent data are only one measure of early-stage innovation activity in pharmaceutical markets, the data seem to point to continued interest in developing AM drugs. We acknowledge that the quality of these patents may also be changing over time. Despite the observed upward trend in the number of patents published, the trend for patent quality—if defined as patents for novel AM drug compounds—might be the reverse.[2] Further

[2] Several studies have shown that there is large degree of inherent variability in published patent quality and different perspectives on what actually constitutes "quality" (Guerrini, 2014; Khanna, 2019).

research is needed to assess the quality of the patents and to determine who is filing these patents to better interpret these observed trends.

ES.4 EXPERT INTERVIEWS

Our expert interviews provided additional perspectives about current challenges and possible interventions to address these challenges in AM drug markets. We asked questions about challenges specific to the U.S. market, as well as questions about eight additional topics to explore AM drug market challenges not addressed during our previous research, as well as other potential interventions that might encourage novel AM drug development. Some of the recommendations made are more developed (with initial efforts already underway) and "actionable" than others. A summary of these discussions is provided below.

Challenges Specific to the U.S. AM Market and Potential Government Interventions. Experts noted that one of the greatest challenges for the AM drug market is the structure of the current U.S. pharmaceutical business model, which results in insufficient returns to manufacturers of AM drugs. Suggested interventions included removing AM drugs from the Diagnosis-related Group (DRG) based reimbursement system, decoupling AM drug sales from volume sold, subsidizing post-market activities, and forming a public entity or public-private partnership for AM drug development.

Another challenge discussed by experts is that the clinical trial evidence of recently approved AM drugs does not show whether the new drug performs better than existing AM drugs to treat MDRO infections. Further, good stewardship requires older drugs to be used first (National Academies of Sciences, Engineering and Medicine, 2022). Experts who raised this point noted the importance of testing for superiority of new AM drugs, rather than non-inferiority; focusing on patient outcomes rather than the elimination of the pathogen, developing new platforms for discovering AM drugs, using clinical trial platforms and networks to generate higher quality evidence, and education of physicians about the benefit of new AM drugs over existing drugs.

Some experts also noted that the U.S. market size of drug resistant infections is too small to be of interest to manufacturers and is expected to shrink further with increased stewardship. One expert suggested changing the current for-profit business model to a non -profit one for any AM drugs that are unlikely to earn a profit due to small market size and publicly funding the development of those drugs. The 2022 National Academies report on combating AMR also suggested it might be possible that drugs with a very small market might be natural non-profits (i.e., it is not possible to profit from their sale) and an alternative might be to invest in a non-profit drug development organization (National Academies of Sciences, Engineering, and Medicine, 2022). Another expert suggested that government could help by assisting companies in accessing foreign markets, which see a greater number of cases. This expert noted that the small companies that have developed AM drugs do not have the presence in foreign markets or knowledge of regulatory affairs to access the insurance systems in those countries.

Experts also noted that AMR will need continued attention. While development of novel AM drugs is essential to treat MDRO infections, strategies must also be employed to combat continued growth of AMR and further growth in MDROs. Expert suggestions to combat AMR included effective oversight of stewardship programs, programs for improvements in hygiene and cleaning, funding research to reduce AMR, working with insurance companies to reduce overprescribing, strengthening surveillance systems, and appropriate use of diagnostics. One expert also noted the importance of relying less on AM drugs and more on developing anti-virulent drugs that interrupt the process of infection in the host.

Other Topics Related to AM Drug Development. Experts were also asked about other topics with respect to AM drug development, including innovation, the role of large companies, potential pull incentives (e.g., market entry reward (MER) models), open-source approaches to AM drug

development, lessons learned from COVID-19, the role of public-private partnerships, stockpiling,, and manufacturing capacity for AM drugs.

Experts noted that governments can encourage innovation in AM drugs by funding clinical trial platforms, clinical trial networks (CTNs), and other forms of partnerships. Development of target product profiles (TPPs) for pharmaceutical developers can also be helpful in encouraging innovation.[3]

Most experts agreed that most large companies have lost interest in the AM drug market because the returns from AM drugs are small compared to other drugs. However, several experts thought that these companies may also see reputational value and recognize the threat of AMR and therefore will continue to be involved in other ways. One such way is the AMR Action Fund, a public-private partnership (PPP)[4] investing in the development of AM therapeutics targeting life-threatening resistant infections.[5]

Push and pull incentives are described and reviewed in detail in the National Academies report on combating AMR and are not described in great detail in this report (National Academies of Sciences, Engineering and Medicine, 2022);instead we asked experts' opinions about a few types of pull incentives, including market entry reward (MER) models.[6]. Some experts were supportive of MER models whereas others noted significant challenges that still need to be addressed, including the complexity of full de-linkage of AM drug sales and volume, lack of accessibility for small companies, lack of clarity in MER procurement, difficulty in establishing eligibility criteria and reward amounts, inability to sustain AM drug development, need for quality clinical evidence, insufficient support for post-approval requirement expenses, cost, and lack of improved patient access. During these discussions, one expert also mentioned that the New Technology Add-on Payments (NTAP) mechanism, which provides additional reimbursement for some novel AM drugs, has recently worked for some hospitals, and should be explored further. Interestingly, experts we interviewed in 2018 said this mechanism had been generally unsuccessful. However, experts we interviewed in 2022 noted that NTAP had recently become easier to access, which might explain this difference in opinion.

When asked about the possibility of an open source approach to AM drug development, experts unanimously agreed that the open source approach to AM drug development — in which all data and ideas are shared without intellectual property (IP) protection— would not be realistic given the importance of IP protection to the AM drug market and to pharmaceutical innovation.

Experts were also asked whether the COVID-19 pandemic provided any useful lessons for stimulating AM drug development to combat AMR. Although the market for AM drugs is much smaller and vaccine development is vastly different from AM drug development, experts noted that

[3] According to the World Health Organization (WHO) a target product profile (TPP) "outlines the desired 'profile' or characteristics of a target product that is aimed at a particular disease or diseases. TPPs state intended use, target populations and other desired attributes of products, including safety and efficacy-related characteristics" and can help guide research and development activities (World Health Organization, 2022).

[4] A public-private partnership (PPP) is a collaboration between a government agency and a private entity to provide a public asset or service. In a PPP, the private party takes on significant risk and management responsibility for the project. It is typically a long-term contract.

[5] The mission of the AMR Action Fund is to develop and introduce two to four new AM agents within the next ten years, and to create a sustainable system for investing in and promoting innovation in this field to address the threat of growing resistance (AMR Action Fund, 2022).

[6] These involve financial rewards made to the developer or intellectual property (IP) holder for obtaining regulatory approval for marketing an AM drug that meets pre-defined criteria, such as novelty, ability to treat a life-threatening resistant infection, etc.

the pandemic response to COVID-19 showed the potential success of public-private partnerships (PPPs), such as those between the U.S. government and Moderna. Other lessons learned from COVID-19 included the value of the high level of clinical evidence generated for the vaccines and the transparency of government in its actions, as these factors were very helpful in encouraging use of the new vaccines. A similar focus during novel AM drug development could encourage use of new AM drugs as well. Clinical trial platforms[7] and clinical trial networks (CTNs)[8] surged during COVID-19 and could have potential benefit for AM drug development. Other experts also mentioned the benefits of CTNs based on the success observed during the pandemic.

We asked several questions about the role of PPPs in AM drug development. Several experts recognized the value of PPPs, such as Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and Global Antibiotic Research & Development Partnership (GARDP), in encouraging novel AM drug development. As noted previously, experts discussed the success of PPPs formed during the COVID-19 pandemic and a few also reported on the successes of the TB Alliance.

When asked about whether the government should focus on stockpiling AM drugs experts agreed that stockpiles may not be the best way to address future surge needs or to serve as a pull incentive because of the difficulty of predicting how AMR will evolve over time and the inherent challenge in anticipating which drug and how much of that drug is needed.

When asked about manufacturing capacity for AM drugs for emergency preparedness purposes, all experts felt strongly about the importance of preparing for a surge need for AM drugs. Manufacturing capacity is currently largely located offshore, and government could support development of a U.S. supply chain for the manufacturing of AM drugs, using creative approaches that might, for example, repurpose facilities for other uses when not needed for AM drug manufacturing.

Table E - 1 summarizes the market challenges and possible interventions that experts discussed during our interviews. As noted in the table, some groundwork has already been done on several interventions. These could be further examined to assess the potential benefit of the interventions. Many of the interventions listed are conceptual and need to be developed in greater detail (e.g., forming a new government entity and strengthening surveillance systems). Several proposed interventions are also synergistic and therefore need sequential implementation, whereas others could be implemented simultaneously. For example, diagnostics will be needed for pathogen detection to effectively run CTNs and establish superiority evidence needed by physicians to encourage use of a new AM drug. This may also require the development of new diagnostics if existing diagnostics cannot be used.

[7] A clinical trial platform is a system or infrastructure that supports the conduct of clinical trials. This can include technology for managing and analyzing data, coordinating research activities, and ensuring compliance with regulatory standards. A clinical trial platform may be used to facilitate collaboration among multiple research organizations, and to streamline the process of conducting clinical trials. The goal of a clinical trial platform is to improve the efficiency and effectiveness of clinical research.

[8] A clinical trial network is a group of research organizations that collaborate to conduct clinical trials. This can include hospitals, clinics, academic institutions, and other organizations involved in medical research. The goal of a clinical trial network is to pool resources and expertise to conduct clinical trials more efficiently and effectively. By working together, clinical trial networks can increase the scope and reach of clinical research and improve the speed at which new treatments are developed and tested.

Table E - 1. Possible Interventions to Address AM Market Challenges as Suggested by Experts Interviewed in 2022

Market Challenge	Intervention	Existing Data to Support Intervention
Market structure, conduct, and performance of the U.S. AM drug industry	Remove AM drugs from the DRG reimbursement system	Some success with the NTAP system
	Change to a market model delinked from sales	UK/Sweden testing these market models
	Subsidies (e.g., in form of priority vouchers)	Already in use to encourage development of drugs for neglected diseases
	Formation of new public entity to manage AM drug portfolio	
Insufficient clinical evidence on added clinical benefit at time of regulatory approval	Use of diagnostics and clinical trial networks	HIV Clinical Trial Networks, National Cancer Institute National Clinical Trials Network
	Test for superiority rather than non-inferiority	
	Focus on patient outcomes rather than pathogens	
	Develop new platforms for discovering new drugs	
	Provide information to physicians about AM drugs	
Small market size – relatively low number of drug-resistant infections in the U.S.	Categorize some AM drugs as not profitable and use a not-for-profit business model for development	
	Assist small drug companies with access to larger foreign markets.	
Threat of an increase in antimicrobial resistance (AMR)	Development of diagnostics	Employed by other countries to manage AMR (e.g., Norway and Sweden)
	Greater oversight of stewardship programs	
	Strengthening surveillance systems	
	Increased investments in policies that combat AMR (e.g., limiting use of AM drugs in agriculture, improvements in hygiene)	
	Development of anti-virulent drugs	

1 INTRODUCTION

The consensus view among many stakeholders is that not enough antimicrobial (AM) drugs are being developed to address current and future drug-resistant infections. There are scientific, economic, and regulatory challenges in the U.S. market that have impeded the development of novel AM drugs. It is important to understand these challenges and to identify new ways to encourage development of novel AM drugs because there are few available treatments for multi-drug resistant organism (MDRO) infections that occur in U.S. hospitals.

1.1 NOVEL AM DRUG DEVELOPMENT IS NOT KEEPING PACE WITH NEED

A unique and major challenge to the AM drug market is that of AMR. Any use of AM drugs can lead bacteria or fungi to evolve resistance to those drugs (Moran, 2019). The decision to use AM drugs however does not incorporate the social cost of the depletion of AM drug effectiveness. AMR can be addressed in a variety of ways, including social, cultural, and economic factors (Minssen, et al., 2020). For example, disease prevention and response, infection control, and stewardship are all effective ways to reduce AMR.

Development of novel AM treatments, however, is essential to treat patients with MDRO infections. The preclinical pipeline and to some extent the clinical pipeline look promising according to experts we interviewed and a recent WHO report (WHO, 2021), but it is a common concern that the current pipeline may not yield enough novel AM drugs to address the bacterial pathogens that are developing resistance or may do so in the future (Hutchings, et al., 2019; Shlaes & Bradford, 2018). Furthermore, while additional treatments for most drug resistant infections exist if first-line treatments fail, many of these have serious side effects (CDC, 2021).

In 2018, we interviewed a variety of stakeholders to examine how drug companies and investors decide to invest in developing new AM drugs, how health care providers determine the value of and decide to prescribe AM drugs, and what barriers exist to increased investment in AM drugs (Eastern Research Group, Inc., 2018). Most of the doctors interviewed described a need at their institution for new AM drugs. Many said that their prescribing options are often restricted due to patients being allergic (or saying they are allergic) to many AM drugs. Having more AM options—particularly more oral AM drug options—to prescribe to patients with allergies would be immensely helpful. Often the only viable AM drugs for patients with allergies are IV-only formulations that cause the patient to stay in the hospital. Based on our interviews of doctors in 2018, another reason doctors need more AM drug options is the perceived increase in prevalence of MDROs in urban settings. Not having enough viable options to treat resistant infections can lead doctors to prescribe medications that have substantial side effects. For example, some doctors have resorted to using older AM drugs like polymyxin to treat resistant infections, even though polymyxin can cause kidney failure. Thousands of patients are treated with these older AM drugs each year and, in addition to the quality of life impacts for the patients, hospitals have to bear the significant costs of dealing with the side effects, such as putting children on dialysis.

1.2 MARKET FAILURE IS THE NORM FOR ALL BIOPHARMACEUTICAL MARKETS

The difficulties encountered in the AM drug market are often characterized in the literature as a market failure. Given that no drug markets are perfectly competitive and are all subject to market failure, we focus here on articulating the market challenges that are specific to AM drugs.

According to economic theory, a perfectly competitive market, comprising producers and consumers each acting in their own self-interest, yields an optimal allocation of goods and services. However, for a market to be considered perfectly competitive, four conditions must be present: (1) there needs to be a large number of producers and consumers of the good or service in question, with no producer or consumer having any influence on the market; (2) both producers and

consumers should be able to enter or exit the market without any restrictions; (3) an enforceable property rights system needs to be in place, such that the good or service is not free (i.e., consumers need to pay to use the good or service); and (4) there should be no informational asymmetries, i.e., both consumers and producers have access to all relevant information, such as prices and costs, to make rational decisions about the good or service being bought and sold (Rattinger, et al., 2008). A market failure results when at least one of these conditions is violated, leading to a net social welfare loss (the market provides a sub-optimal quantity of the good or service). Situations that violate one or more of these conditions include (Bækkeskov, 2019):

- *Increasing economies of scale in production*. When economies of scale increase regardless of production, market forces lead to monopoly production, resulting in suboptimal levels of production and consumption.

- *Public goods*. Private markets underinvest in goods that are non-excludable (no person can be excluded from using it), non-rival (one person using the good does not prevent another from using it), and non-rejectable (no person can reject using the good) even though these goods are socially beneficial.

- *Production or consumption externalities*. Production and/or consumption of certain goods can create unintended consequences for third parties not involved in the market transaction. Because the free-market costs and prices, which are based on the laws of supply and demand, do not account for these impacts, markets allocate resources toward negative externalities and away from positive externalities, relative to the social optimum.

- *Risk and uncertainty*. When there is risk or uncertainty associated with the production or consumption of a good or service, a market may fail to emerge due to transaction costs or asymmetry of information.

Perfectly competitive markets serve as a benchmark for economic performance, but rarely exist in real life. Thus, market failure, as defined above, is not an exception but the norm for most markets, and the biopharmaceutical market is no exception due to several factors. First, the number of producers in the biopharmaceutical market for a given drug is limited (for brand drugs, there is only one producer) and there is no perfect substitute for the drug. Further, entry barriers, such as large capital investments needed for research and development, patents, and FDA-granted exclusivities, can preclude other producers from entering a market for several years. Combined, these structural characteristics of the biopharmaceutical market enable innovator firms (i.e., producers of brand drugs) to realize "…higher profits than would be possible in a purely competitive marketplace with many producers" (Rattinger, et al., 2008). It is often argued that such high profits are needed to incentivize producers to invest in research and development for new biopharmaceuticals to improve public health. Second, there is informational asymmetry among the producer, prescribers (clinicians), and consumers (patients) of a given drug. Incomplete and/or inaccurate information about a given drug could lead to suboptimal market outcomes. Third, federal and state governments influence buying and selling of a given drug through supply side regulations, such as research and development tax credits, orphan drug development tax credit, etc., and demand-side regulations, such as Medicare Part B, Part D, and Medicaid programs. Additionally, third-party insurers aim to get "…patients to use those drugs that are deemed necessary and cost effective to a greater extent" (Rattinger, et al., 2008) through various cost-sharing mechanisms, such as coinsurance, deductibles, tiered formularies, and prior authorization. These all influence the price and ultimately the supply as well as the demand for a given drug.

1.3 AM DRUG DEVELOPMENT HAS UNIQUE MARKET CHALLENGES

By virtue of being a biopharmaceutical market, the AM drug market is not a perfectly competitive market and subject to market failure. Market failure is therefore not a condition unique to the AM drug market. What is unique about the market for AM drugs is that it is associated with a positive externality (public health)[9] as well as a negative externality (antimicrobial resistance or AMR) (Mossialos, et al., 2010). The positive externality arises because the use of a given AM drug by one patient reduces the chance of others catching that strain of bacteria from that patient. Additionally, the use of the given AM drug reduces the development of resistance to other AM drugs and could prevent cross-resistance within existing classes of AM drugs (Simoens & Spriet, 2021). On the negative side, when one patient uses an AM drug, a small number of bacteria become resistant to the treatment; the patient can then transmit resistant bacteria to others. Because such resistant bacteria will have a strong selective advantage over time, eventually other people will be unable to benefit from the use of the same AM drug, further perpetuating the problem and creating a negative externality. This negative externality could also be amplified through development of cross-resistance with the use of the AM drug in question, reducing the effectiveness of other AM drugs. One way to mitigate this negative externality is to introduce novel AM drugs that can treat resistant drug infections, which is discussed further below.

2 STUDY OBJECTIVES

Novel AM drugs are needed to deal with AMR, yet many of the recently approved AM drugs are primarily derivatives of existing AM drugs. Furthermore, there are only a few new AM drugs against the MDROs listed on the WHO priority list (Dall, 2021). These MDRO infections are typically treated at hospitals, which creates additional challenges associated with reimbursement, as described in detail below. This report focuses on the scientific, economic, and regulatory challenges that impede the development of novel AM drugs needed to treat MDRO infections, as well as potential interventions that could address these issues.

The report begins with a discussion of quantifying the AM market externalities; trends in early AM drug discovery are then explored through an analysis of patents. The report then summarizes prior research on scientific, economic, and regulatory challenges in the AM drug market. Finally, the report describes the results of expert interviews on several new topics related to market challenges for AM drug development, including experts' opinions on potential options to address those challenges.

3 METHODOLOGY

We first conducted a scoping review of the literature published in the last 10 years to identify studies that provide empirical evidence of the negative externality posed by AMR in the U.S. AM drug market. We searched PubMed, Google Scholar, and the grey literature via Google, using a variety of search term combinations, such as market failure, market challenges, market inefficiencies, antibiotic, antimicrobial, quantification, and interventions. In addition, we reviewed the cited references to identify additional literature of interest.

We also examined whether there has been a slowdown in the intensity of early stage AM drug discovery by looking at the number of AM drug compound patents filed and/or granted annually over the last 30 years using Espacenet's searchable patent database. We then compared the early stage AM drug discovery trends to that of the non-AM biopharmaceutical market (i.e., all drugs, except for AM drugs grouped together) to evaluate: (1) whether there is a slowdown in

[9] All infectious disease drugs, not just AM drugs, have positive externalities because their use reduces the chance of transmitting disease to others.

early-stage AM drug discovery and (2) whether any slowdown is specific to AM drug discovery or more systemic across the industry.

We also conducted a review of the recent literature on the scientific, economic, and regulatory challenges encountered in the AM drug development market in the U.S. We supplemented this literature review with findings from a 2018 study for which we conducted a series of semi-structured interviews with AM experts, including early stage developers, venture capitalists, doctors, and hospital representatives, to examine: (1) how drug companies and investors decide to invest in developing new AM drugs; (2) how health care providers determine the value of and decide to prescribe AM drugs; and (3) what barriers exist to increased investment in AM drugs.

Next, we conducted another series of semi-structured interviews with experts from different organizations to explore the inefficiencies in the AM drug market not addressed during our previous research, as well as potential strategies for alleviating these inefficiencies (see Appendix A for our interview questions). These groups included academics, biopharmaceutical companies, foundations, payers/health technology assessment (HTA) groups, and others (Table 1).

Table 1. Anonymized List of Experts Interviewed in 2022, by Group

Group	Job Title	Expert
Group 1 – Academia	Professor	Academic 1 (A1)
	Professor	Academic 2 (A2)
	Professor	Academic 3 (A3)
	Professor	Academic 4 (A4)
	Postdoctoral fellow	Academic 5 (A5)
Group 2 – Biopharmaceutical Company	CEO	Biopharmaceutical Company 1 (BC1)
	CEO	Biopharmaceutical Company 2 (BC2)
	CEO	Biopharmaceutical Company 3 (BC2)
Group – 3 Foundation	Director	Foundation 1 (F1)
Group 4 – Payer/HTA	Program Director	Payer/HTA 1* (P1)
	Consultant Clinical Advisor	Payer/HTA 2* (P2)
Group 5 – Other	Senior Advisor at a Public Health Agency	Other 1 (O1)
	Subject Matter Expert/CEO	Other 2 (O2)
	Senior Clinical Subject Matter Expert	Other 3 (O3)
	Director of a Public Health Organization	Other 4 (O4)
	Clinical Trials Network Principal Investigator	Other 5 (O5)

*Two individuals at the same organization

4 FINDINGS

4.1 QUANTIFICATION OF THE AM DRUG MARKET EXTERNALITY

As noted in Section 1, the AM drug market is characterized by both the positive externality of public health improvements and the negative externality of AMR. The AM drug market is unique in that AM drugs are the only drugs that fully cure patients yet become less effective the more they are used (Nathan, 2020). The net effect of the positive and negative externalities on the market for AM drugs remains uncertain. A recent report by the National Academies of Sciences, Engineering and Medicine (NASEM) noted that there are challenges in measuring morbidity and mortality in drug resistant infections (National Academies of Sciences, Engineering, and Medicine, 2022). For example, the same drug resistant infection can have very different outcomes if it is acquired in or outside of a hospital, in a low income or high income country, or acquired by a person elderly or in poor health. Some published studies have attempted to quantify these externalities in the U.S.

(Naylor, et al., 2018; Johnson, et al., 2019; Thorpe, et al., 2018). The estimates for the AMR externality in the U.S. in these studies are listed in Table 2 and are highly variable. Monetized estimates range from as low as $10,800 for patient treatment costs attributable to a MRSA infection to over $3.6 billion for national treatment costs associated with MDRO infections, to $13.8 billion in societal costs due to MRSA (Table 2). The variation in these estimates is attributable to definitional differences in the exposure (e.g., type of AMR) and outcome (e.g., excess length of hospital stay) variables; inconsistent treatment for confounding factors, such as patient characteristics, severity of disease, and timing of infection; differing valuations of hospital bed days (accounting versus opportunity cost); and choice of counterfactual, i.e., susceptible versus no infection (Wozniak, et al., 2019; Naylor, et al., 2018). The extent of the AM drug market externality, while potentially significant, is therefore difficult to characterize. However, it is possible to qualitatively assess and analyze the unique challenges to the AM drug market and evaluate possible interventions that have the potential to address concerns about the suboptimal number of commercialized AM drugs to address AMR.

Table 2. Quantification of the AMR Externality in the United States[10]

Type of AMR Exposure	Counterfactual	Type of Outcome	Estimate (2022$)	Source
Methicillin resistant *Staphylococcus aureus* bacteriuria (MRSA)	Methicillin susceptible *Staphylococcus aureus* bacteriuria (MSSA)	12-month mortality	MRSA was not associated with mortality (in the univariate analysis) with p=0.107	(Mohajer & Musher, 2013)
Ampicillin resistant *E. coli* bloodstream infection	Ampicillin susceptible *E. coli* bloodstream infection	Main outcome is 30-day mortality and secondary outcomes include 7-day mortality and mortality at discharge	Resistance was not significantly associated with 30-day mortality [OR= 1.37 (95% CI; 0.39,4.77)] and was not significantly associated with other outcomes including 7-day mortality [OR=1.25 (95% CI; 0.35, 4.39)] and in-hospital mortality [OR=1.74 (95% CI; 0.65, 4.67)]	(Bergin, et al., 2015)
Carbapenem-Resistant *Klebsiella* bacteraemia	Non-Carbapenem-Resistant *Klebsiella* bacteraemia	30-day mortality	Carbapenem non-susceptibility was significantly associated with 30-day mortality [OR = 9.08 (95% CI, 1.17–70.51) p = 0.04]	(Biehle, et al., 2015)
MRSA post-partum breast abscess	MSSA post-partum breast abscess	Direct medical cost and healthcare utilization	Health services utilization was similar among case patients with MRSA and MSSA, however, MRSA cases had significantly more outpatient visits (median 6.0 versus 3.0). There was no significant cost difference between patients with MRSA infection and those with MSSA. Attributable costs (in 2012 USD) were similar regardless of methodology used - Mean Attributable Hospital Direct Costs= $507 (95% CI;-818, 1842), p= 0.45 for MRSA vs MSSA. [Results also presented using a Medicare unit cost and partial costing, nonsignificant]	(Branch-Elliman, et al., 2012)
Heterogeneous vancomycin-intermediate (hVISA) MRSA bloodstream infection	Vancomycin susceptible MRSA bloodstream infection	30-day mortality, MRSA-infection related mortality and Length of Stay (LoS) (total and after onset)	Thirty-day non-hVISA MRSA infection-related mortality was not significantly different to hVISA cases (p=0.081), also all-cause 30-day mortality was not significantly different (p=0.076). hVISA was significantly associated with longer total hospital LoS (median difference of 8 days, p =	(Castón, et al., 2014)

[10] All the studies cited in Table 2, except for the last two, were described and evaluated in Naylor et al. (2018). The information we provide in Table 2 is based on the data provided on these studies by Naylor et al. (2018).

Type of AMR Exposure	Counterfactual	Type of Outcome	Estimate (2022$)	Source
			0.022) and longer LoS after the onset of infection (median difference of 9 days, p=0.021)	
Resistant infections - multiple species	Non-resistant infections	Resistant infection related deaths	Estimates the minimum number of illnesses and deaths caused by antibiotic resistance to be 2,049,442 and 23,000 respectively annually	(CDC, 2013)
Carbapenem- and ampicillinsulbactam-resistant *A. baumannii* bloodstream infections	Carbapenem- and ampicillinsulbactam-susceptible *A. baumannii* bloodstream infections	In-hospital mortality	Resistance was not significantly associated with in-hospital mortality [OR= 1.15 (95% CI; 0.51 to 2.63),p=0.74]	(Chopra, et al., 2013)
Invasive MRSA infection.	Invasive MSSA infection	In-hospital, 7-day and 30-day mortality	MRSA did not significantly affect mortality for any of the used mortality measures. Results presented are for in-hospital, 7-day and 30-day mortality respectively; RR= 1.19 (95% CI; 0.96-1.49), RR = 0.90 (95% CI; 0.65-1.24), RR = 1.15 (95% CI; 0.90-1.46)	(Ericson, et al., 2015)
Second-line drug (SLI) and fluoroquinolone resistant tuberculosis	SLI and fluoroquinolone susceptible tuberculosis	Mortality and survival	Resistance to SLIs after 8 months of treatment was significantly associated with higher mortality (HR, 2.8; 95% CI, 1.4–5.4). Fluoroquinolone resistance was significantly associated with lower survival (p = 0.03)	(Ershova, et al., 2014)
Fluconazole & caspofungin resistant *Candida glabrata* hunfaemia	Fluconazole & caspofungin susceptible *Candida glabrata* hunfaemia	28-day and in-hospital all-cause mortality	Resistance was not significantly associated with 28-day mortality in the multivariate analysis	(Farmakiotis, et al., 2015)
MDR *Acinetobacter calcoaceticus-A. baumannii*	Non-MDR *Acinetobacter calcoaceticus-A. baumannii*	Main outcome is 30-day mortality and secondary outcomes include 14-day mortality and clinical outcomes such as LoS	MDR was not significantly associated with 30-day mortality in the multivariate analysis [OR not given] but was associated with increased LoS in univariate comparison [11.5 vs 6, p=0.01].	(Fitzpatrick, et al., 2015)
Vancomycin resistant enterococci (VRE)	Non-VRE bloodstream infection	Mortality & hospital cost	Impact on survival was not significant (HR= 1.9 [95% CI, 0.87–5.1], p=0.1). Total median hospital costs were significantly higher for	(Ford, et al., 2015a)

Type of AMR Exposure	Counterfactual	Type of Outcome	Estimate (2022$)	Source
bloodstream infection			patients with resistant infections ($172,000 vs. $86,000, p= 0.0003), largely due to increased median LoS (42 vs. 29 days, p= 0.0005). (Year of USD unclear, taken as last study year – 2012)	
VRE blood stream infection (BSI)	Non-VRE bloodstream infection	LoS and hospital cost	No significant differences were seen in 3-month mortality with and without VRE BSI (0% vs. 2.1%, respectively). Median LoS was significantly longer for patients with VRE BSI than for colonized patients without BSI (24 vs. 20.5 days, p = 0.04). Median costs were not significantly higher with VRE BSI ($61,151 vs. $54,992, p=0.34). VRE colonized and non-colonized patients without VRE BSI had no significant difference in LoS and there were no differences in 1-year survival (92% vs. 90% for VRE-positive and VRE-negative patients). [Comparators were not always clear].	(Ford, et al., 2015b)
Carbapenem resistant community- and health care-associated *P. aeruginosa* bacteremia	Carbapenem susceptible community- and health care-associated *P. aeruginosa* bacteremia	30-day mortality	Resistance was associated with a non-significant increase in 30-day mortality [HR=1.53, (95% CI;0.68-3.42),p=0.3]	(Hattemer, et al., 2013)
MRSA Ventilator Associated Pneumonia	Non-exposure Ventilator Associated Pneumonia	Ventilator days, ICU LoS, hospital LoS, and mortality	Resistance was not associated with different outcomes. Resistance was not an independent predictor of mortality [OR= 0.815, (p = 0.59)]. ICU LoS was 24 vs 23 days (p=0.804) and hospital LoS was 34 vs 35 days (p=0.756) for MRSA vs non-MRSA respectively	(Hill, et al., 2013)
MRSA Cardiac Implanted Electronic Device-Related Infective Endocarditis	Non-"MRSA" Cardiac Implanted Electronic Device-Related Infective Endocarditis	Mortality	MRSA was associated with mortality (p<0.001) in the survival analysis, the logistic regression found MRSA to be an independent predictor of mortality [OR=0.158 (95% CI; 0.047–0.534) p = 0.003]	(Kim, et al., 2014)
XDR/MDR *A. baumannii* infection	Susceptible *A. baumannii* infection	30-day mortality	XDR was associated with a greater risk of death [(OR=7.0 (95% CI 1.1–44.1), p = 0.047)]	(Kitazono, et al., 2015)

Type of AMR Exposure	Counterfactual	Type of Outcome	Estimate (2022$)	Source
Nalidix, ceftriaxone and multidrug resistant nontyphoidal salmonella infection	Non-exposure nontyphoidal salmonella infection	Death, LoS > 3 days, and clinical outcomes such as diarrhoea	Risk of a hospital stay greater than 3 days was 2 times higher (95% CI 1.3–3.0) for patients with infections resistant to 5 antimicrobial classes, 1.7 times higher (95% CI 1.1–2.7) for those resistant to at least ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline ACSSuT, and 1.9 times higher (95% CI 1.2–3.2) for ACSSuT-only resistance. Only 1 patient died so there are no results presented on risk of death.	(Krueger, et al., 2014)
Community associated-MRSA	No community associated-MRSA	Third-party payer and productivity cost (including from caregivers)	Third-party payer costs of up to $478 million-$2.2 billion and economic costs of up to $1.4–$13.8 billion annually	(Lee, et al., 2013)
ESBL-producing *E. coli* and *Klebsiella* species Urinary Tract Infections	ESBL-negative *E. coli* and *Klebsiella* species Urinary Tract Infections	Median LoS, median cost, hospital monetary loss and infection-related mortality	No significant differences were found in infection-related mortality rates (p=0.37), median LoS was significantly longer (6 days (IQR; 4–8) vs 4 days (IQR; 3–6) p=0.02), as was total hospital cost 10,741 USD (IQR; 6846–15,819) vs 7,083 USD (IQR; 5667–11,652) p=0.02. Median differences in cost and reimbursement between ESBL-producers vs non–ESBL-producers were 3658 USD (p=0.02) and 469 USD (p=0.56), median loss per patient with ESBL-*E. coli* or *Klebsiella* infection was 3189 USD (2011-2012 USD)	(MacVane, et al., 2014)
MRSA bacteremia	MSSA bacteremia	30-day and 90-day mortality (methicillin resistant)	No significant difference in either outcome; for 30-day mortality OR=0.62(95% CI; 0.15-2.61) p=0.52, for 90-day mortality OR=0.51 (95% CI; 0.12 - 2.14), p=0.36	(Manandhar, et al., 2016)
Fluconazole resistant Gram-negative rod bacteraemia	Fluconazole susceptible Gram-negative rod bacteraemia	30-day all-cause cumulative mortality (& risk of death)	Resistance was significantly associated with mortality (p=0.018) and increased risk of death (HR 2.11 (1.06 - 4.23))	(Miles-Jay, et al., 2015)
Healthcare associated MRSA infections	No MRSA infection inpatient	Length of stay and costs (Fixed and variable inpatient costs,	Excess length of stay estimates were 17.64 (95% CI; 17.58-17.71, p< 0.0001) days, 11.43 (95% CI; 10.44- 12.43, p < 0.0001) days and 13.97 (95% CI; 10.49-17.44,p < 0.0001) days for the	(Nelson, et al., 2015a)

Type of AMR Exposure	Counterfactual	Type of Outcome	Estimate (2022$)	Source
		assumed 2010 USD)	conventional, post-HAI and matching methods, respectively. Excess total inpatient cost estimates were $31,570 (95% CI; $30,074 - $33,067, p < 0.0001), $24,015 (95% CI; $10,882 - $37,149,p < 0.0001) and $26,855 (95% CI; $22,583 - $31,126, p < 0.0001) respectively (assumed 2010 USD)	
Healthcare associated MRSA infections	Non-Healthcare associated MRSA infections	Post-discharge healthcare costs and utilization (readmission, antibiotic usage, and hospital days), 365-day follow up	Positive MRSA culture was significantly associated increased inpatient costs of $12,167 (p <0 .0001). Positive MRSA culture was significantly associated with a 13.8% increase in number of prescriptions (p <0.0001), a 39.6% increased odds of having a readmission (Pp<0 .0001), and 20.4% more inpatient days (p <0 .0001) (costs in 2013 USD)	(Nelson, et al., 2015b)
Healthcare-associated MRSA colonization and infections	Non-Healthcare-associated MRSA colonization and infections	Post-discharge mortality (post-discharge 365 day mortality)	MRSA infection had a significant impact on post-discharge mortality (for the full cohort HR = 1.489, 95% CI; 1.261 - 1.758, p =0<.0001, for the matched cohort HR = 1.464, 95% CI; 1.212 - 1.769, p <.0001).	(Nelson, et al., 2015c)
Carbapenem resistant nonbacteremic *K. pneumoniae* infections (pneumonia and UTI)	Non-carbapenem-resistant, non-ESBL-producing nonbacteremic *K. pneumoniae* infections (pneumonia and UTI)	In-hospital mortality, 90-day mortality, 30-day readmission	Resistance had a non-significant and positive impact on in-hospital mortality (14% vs 10%; p =0.76), 90-day mortality (24% vs 14%; p=0.31) and 30-day readmissions (32% vs 19%; p = 0.21).	(Ny, et al., 2014)
Gram-negative bacilli susceptible to <=1 antibiotic	Gram-negative bacilli susceptible to vs >=2 antibiotics	7-, 15- and 30-day mortality	Resistance (case status) was not significantly associated with mortality for any time point (7-,15- and 30-day mortality; p= 0.87, 0.20 & 0.14 respectively)	(Patel, et al., 2014)
High carbapenem MIC Enterobacteriaceae infections	Low carbapenem MIC Enterobacteriaceae infections	30-day mortality, LoS and ICU LoS	Cases with carbapenem MICs of 2, 4, and 8 mg/liter had significantly higher 30-day mortality than those in the group with carbapenem MICs of 1 mg/liter (p = 0.04). The	(Patel & Nagel, 2015)

Type of AMR Exposure	Counterfactual	Type of Outcome	Estimate (2022$)	Source
			high-MIC group was associated with decreased overall survival by Kaplan-Meier log rank test (p=0.01). Mean total hospital LoS was longer but not significantly (57.6 days vs 34.4 days, p= 0.06), mean ICU LoS was significantly longer (56.6 days vs 21.7 days, p=0.01) in the group with MICs of 2 to 8 mg/liter than in the group with MICs of 1 mg/liter.	
Carbapenem-resistant *K. pneumoniae* infections	Carbapenem-susceptible *K. pneumoniae* Infections and no Klebsiella Pnuemoniae Infection	Post-transplant survival	Resistance did not significantly impact mortality compared to susceptible strains, comparing the confidence intervals that results from modelling each of these groups against no *Klebsiella* infection [CRKP HR = 6.92 (95% CI, 3.24- 14.79) and susceptible infection HR = 3.84 (95% CI, 1.86-7.94)]	(Pereira, et al., 2015)
Carbapenem-resistant *K. pneumoniae* bacteriuria	None	Development of secondary healthcare associated infection	Resistance not associated with secondary healthcare associated infections (which were notably absent)	(Qureshi, et al., 2014)
Drug-resistant Streptococcus pneumonia	Susceptible Streptococcus pneumonia	Annual and incremental cost burden. Included: 1) direct costs (including medical care), 2) costs from adverse outcomes, 3) work-loss costs, and 4) cost from lost wages	Resistance was estimated to account for 4% (2012 $91 million) of annual pneumococcal pneumonia direct medical costs and 5% ($233 million) of total costs (including work and productivity loss). Most of the incremental medical cost ($82 of $91 million) was estimated to be due to hospitalizations resulting from erythromycin resistance. Increased resistance to erythromycin was associated with the greatest projected cost	(Reynolds, et al., 2014)
MRSA bacteraemia following pneumonia	Non-MRSA bacteraemia following pneumonia	In-hospital all-cause mortality, hospital LoS	MRSA bacteraemia was not an independent factor for mortality but had a trend towards this [OR = 1.56; 0.93 - 2.61]. MRSA bacteraemia was associated with additional LoS of 10.3 days (95 % CI 6.7 to 13.9 days, $p < 0.001$).	(Shorr, et al., 2015)

Type of AMR Exposure	Counterfactual	Type of Outcome	Estimate (2022$)	Source
Carbapenem resistant *K. pneumoniae*	Carbapenem susceptible *K. pneumoniae*	Mortality	Resistance was significantly associated with death in all the models [HR= 8.8 (95% CI; 2.2–35.8), p=0.002 in the unadjusted Cox model)	(Simkins, et al., 2014)
VRE infection	No VRE infection	Mortality (time from transplant to all-cause death)	VRE- bacteraemia was significantly associated with worse mortality [HR= 4.28, (95% CI 3.23–5.66) P<0.001] in multivariable analysis.	(Tavadze, et al., 2014)
MDR Ventilator associated pneumonia	Non-MDR Ventilator associated pneumonia	28-day survival, hospital mortality, LoS (hospital & ICU)	Resistance was significantly associated with 28-day survival (p=0.006), hospital LoS (37 vs 31 median days, p=0.07), ICU LoS (31 vs 27, p=0.08), however this differed when cases split further into different organism types. In non-fermenting Gram-negative rods [HR=1.37(95% CI: 0.62-3.06)], there was no association between MDR and in-hospital mortality, but, in all other organisms, MDR was significantly associated with increased mortality [HR= 6.15 (95% CI: 1.80-21.05) p = 0.004].	(Tedja, et al., 2014)
General resistance to standard prophylactic antibiotics	No resistance	Infection-related mortality	Between 38.7% and 50.9% of pathogens causing surgical site infections and 26.8% of pathogens causing infections after chemotherapy were resistant to standard prophylactic antibiotics in the USA. A 30% reduction in the efficacy of antibiotic prophylaxis for these procedures would result in 6,300 infection-related deaths (2,100 for a 10% reduction – 15,000 for a 70% reduction). 13, 120 infections (42%) per year after prostate biopsy were attributable to fluoroquinolone resistance.	(Teillant, et al., 2015)
Caspofungin resistant and MDR Candidaemia	Susceptible Candidaemia	30-day and 14-day all-cause mortality	Caspofungin resistance was significantly associated with mortality [14-day mortality - HR = 3.02 (95% CI; 1.28–7.09), p=0.011, 30-day mortality - HR= 2.96 (95% CI; 1.38–6.37), p=0.05], MDR was significantly associated with mortality [14-day mortality HR=3.02 (1.27–7.14), p=0.012, 30-day mortality HR= 2.86 (95% CI; 1.31–6.21), p=0.008]	(Wang, et al., 2015)

Type of AMR Exposure	Counterfactual	Type of Outcome	Estimate (2022$)	Source
Ceftriaxone-resistant *Streptococcus pneumoniae* pneumonia	Ceftriaxone-susceptible *Streptococcus pneumoniae* pneumonia	Clinical cure, (infection-related) LoS, in-hospital mortality, 30-day readmissions	Resistance was not significantly related to any of the outcomes. Results for resistant vs susceptible were: median LoS 17 vs 15, p=0.46, infection-related LoS 9 vs 8 p=0.74, in-hospital mortality p=1.00, and 30-day readmission for pneumonia p=1.00.	(Wenzler, et al., 2014)
Antibiotic-resistant infections	Patients hospitalized without an antibiotic-resistant infection	National inpatient cost estimates of treating antibiotic-resistant infections	National incremental treatment cost of antibiotic-resistant infections is $2.2 billion per year based on 2014 data.	(Thorpe, et al., 2018)
Diagnosed MDRO infections	Patients hospitalized with bacterial infections without diagnosed MDROs	National inpatient cost estimates of infections associated with MDROs	National incremental cost of infections associated with MDROs is estimated to range between $2.39 billion (95% CI; $2.25 to $2.52 billion) for infections coded as MDROs and $3.38 billion (95% CI; $3.13 to $3.62 billion) if infections undercoded for MDROs are counted.	(Johnson, et al., 2019)

4.2 TRENDS IN EARLY STAGE AM DRUG DISCOVERY

To evaluate trends in early stage AM drug discovery and how they compare to non-AM drugs, we used Espacenet's searchable patent database to query the number of patents published for AM and non-AM drug targets per year over the 1990-2021 period. Espacenet is an online platform developed by the European Patent Office (EPO) together with the member states of the European Patent Organisation for searching worldwide. Espacenet's database contains patent information on over 130 million patent documents dating back to 1782 to present (Espacenet, 2022). Each patent and patent application in the database is assigned at least one Cooperative Patent Classification (CPC) code indicating the subject to which the patent or patent application relates. Patents or patent applications relating to the "specific therapeutic activity of chemical compounds or medicinal preparations" (hereinafter referred to as all drug target compounds) are classified under A61P and of those compounds that are anti-infectives are classified under A61P31. Further, the anti-infectives category includes local antiseptics (A61P31/02), antibacterial agents (A61P31/04), antimycotics (A61P31/10), and antivirals (A61P31/12). We compiled the number of patents published per year for CPC codes A61P (all drug target compounds), A61P31 (anti-infective compounds), and A61P31/04 (antibacterial compounds).

Figure 1 below, presents the number of patents published annually for each of the three CPC codes worldwide. The average annual number of patents published over the 1990-2021 period is about 36,000 for all drug target compounds (CPC = A61P); 8,300 for anti-infective compounds (CPC = A61P31); and 3,700 for antibacterial compounds (CPC = A61P31/04). The data show that 2017 has been an inflection point in early drug discovery, even for AM drug compounds, with increases in the number of patents published per year for all three categories from 2017 and onward. The average number of patents published per year during the 2017-2021 period is around 66,600 for all drug target compounds; 13,200 for anti-infective compounds; and 5,700 for antibacterial compounds.

Figure 1. Number of Patents Published Worldwide for A61P (All Drug Target Compounds), A61P31 (Anti-infective Compounds), and A61P31/04 (Antibacterial Compounds), 1990-2021

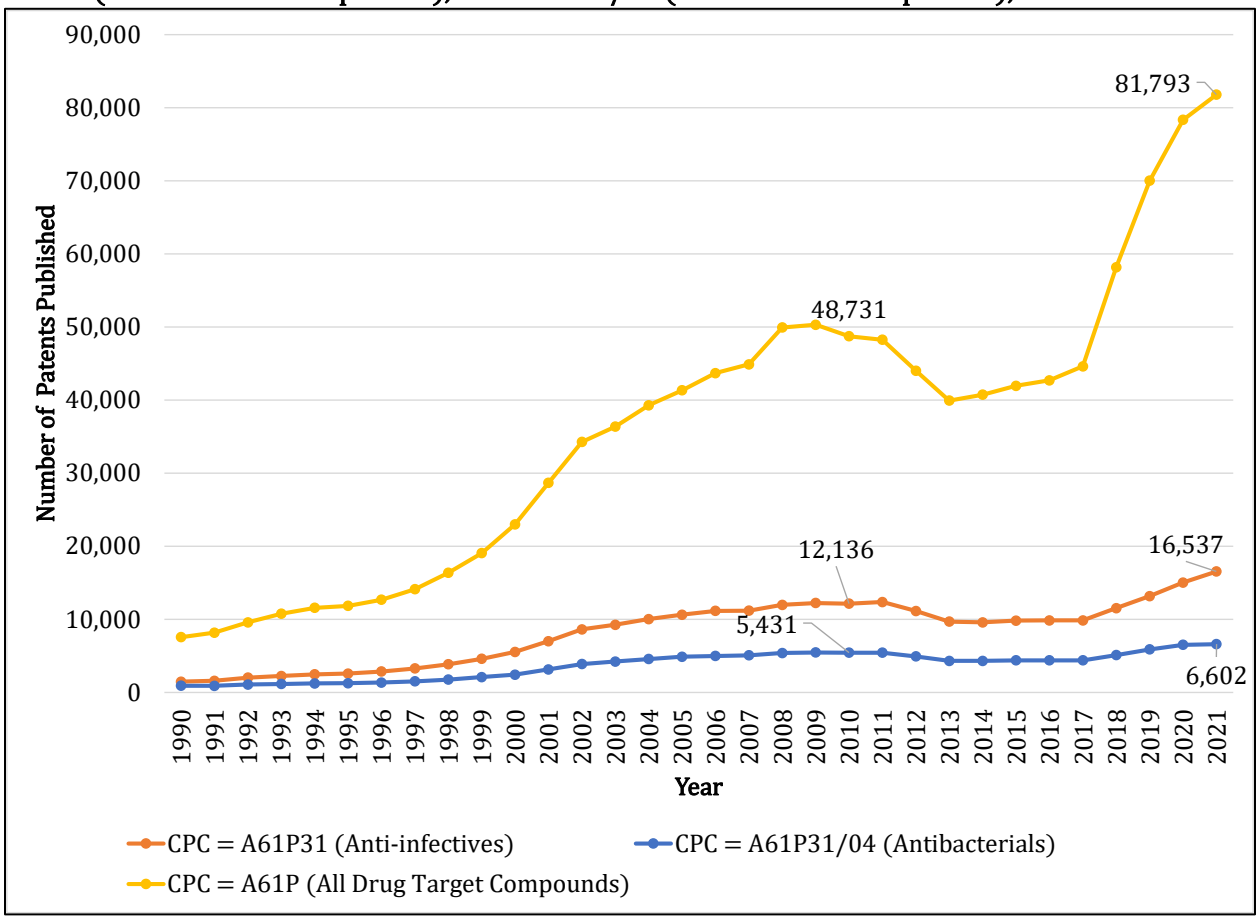


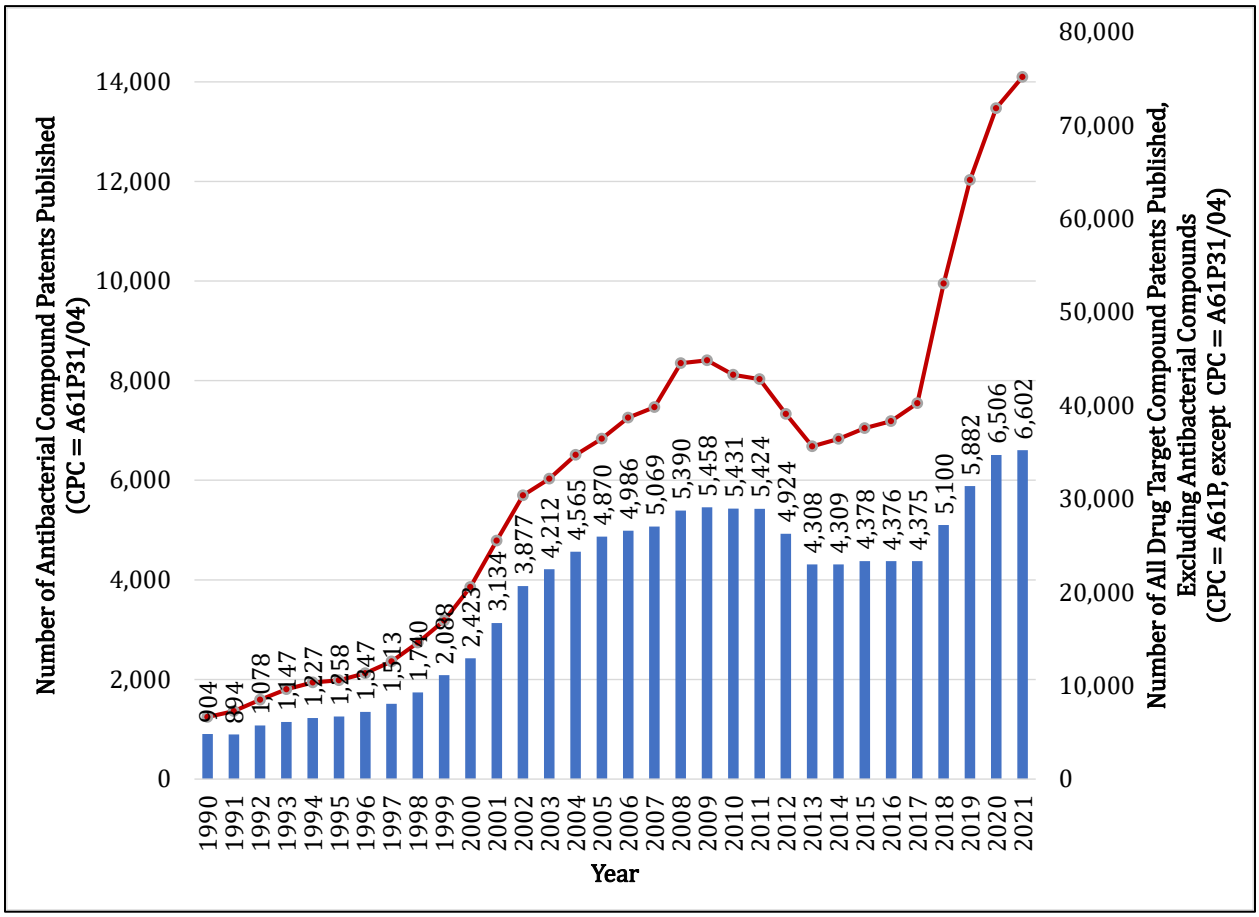
Figure 2 presents annual patent publications for antibacterial compounds (A61P31/04) and all other drug compounds, excluding antibacterials (A61P – A61P31/04). As can be observed in Figure 2, the annual AM drug compound patents, while less volatile from year to year than patents for all other drug target compounds, follow a similar trend. Since 2010, average annual number of AM drug compound patents published increased by 72 percent (from around 3,000 to 5,100 per year), while average number of annual patents published for all other drug compounds increased by 102 percent (from about 23,800 to 48,100 per year). During the same period, there has been around a 2-fold increase in the total number of AM and non-AM drug compound patents published worldwide, (from 62,200 in 2010 to 118,800 in 2021 for AM and from 499,500 in 2010 to 1,033,800 in 2021 for non-AM drug target compounds) implying the rate of discovery for new AM and non-AM drug compounds is similar overall. This partly provides further evidence to the success of push incentives (see Section 4.4.3.2) in keeping at least the non-clinical AM drug pipeline robust.

Over the past 12 years (i.e., since 2010), there have been over 61,600 potential AM drug compound patents published. Even if most of these compounds, for various reasons, do not proceed into pre-clinical research and then to the clinical stage, the volume of patents appears to be large enough to yield a steady stream of new AM drugs over the next 12 years. For example, if we assume that only 0.5 percent of the 61,600 AM drug compound patents proceed into drug

development and, those only have a 16.3 percent chance of regulatory approval (Thomas & Wessel, 2022), this translates to over 50 new AM drugs over the next 12 years.

We acknowledge that the quality of these patents may also be changing. Further research is needed to assess the quality of the patents and who is filing them to fully understand the meaning of these trends.

Figure 2. Number of Patents Published Worldwide for All Drug Target Compounds, Excluding Antibacterial Compounds (A61P -A61P31/04) versus Antibacterial Compounds A61P31/04, 1990-2021



4.3 SCIENTIFIC, ECONOMIC, AND REGULATORY CHALLENGES IN THE AM DRUG MARKET

According to Spellberg (2014), the challenges faced by the AM drug markets can be grouped into three categories, scientific, economic, and regulatory. While we use these categories to discuss the various challenges, we acknowledge that some challenges could be classified in more than one category (e.g., research and development difficulties can be covered both under scientific and economic challenges). This section summarizes the recent literature, including ERG's 2018 study, on each category.

4.3.1 Scientific Challenges

Scientific challenges are those that are encountered with the discovery of new types or classes of AM drugs. No new classes of AM drugs have been discovered since the 1980s, mainly because the science of discovering and developing novel AM drugs is very difficult (Chapman, 2020). There is an urgent need to find new screening methods to discover new AM drugs

(Shaarma, et al., 2021). For example, Zhu et al. (2021) argue that combination therapies (antimicrobials with other drugs, including other antimicrobials) could potentially address the need for new therapies and combination screening technologies are needed to support and advance these efforts. Some advances are also being made. For example, a new antibiotic was recently discovered using artificial intelligence and another was discovered using computational models of bacterial gene products (Wang, et al., 2022; Marchant, 2020). Both these products are in the early phases of development and optimizing these leads to make them investigational new drug (IND) candidates is difficult science (Payne, et al., 2015). The science of gram-negative pathogens also poses a significant challenge because the structure of their cell wall is difficult to penetrate by antibiotics (Pew, 2018). At the same time, some of the AM institutional knowledge at companies has been lost with the dismantling of AM drug programs, resulting in a shortage of expertise (Renwick and Mossialos, 2018).

Another scientific challenge is the lack of diagnostic tests to identify infections more accurately. Lack of good diagnostics makes clinical trials more challenging. Having an effective companion diagnostic for screening patients for clinical trials ensures that patients that would potentially benefit from the therapy can be rapidly identified (Trevas, et al., 2021). Rapid diagnostics can also be used to facilitate appropriate stewardship of AM drug prescribing in clinical settings (Cama, et al., 2021). During our 2018 interviews, we learned that there is still a need for more rapid diagnostic testing devices. Specifically, one area of need, perhaps counterintuitively, is for a rapid diagnostic device for identifying viruses in clinical practice. When doctors are deciding how to treat an infection that could be viral or bacterial and have to choose between prescribing an AM drug or conducting an $800 diagnostic test, doctors may be more inclined to administer the AM drug despite the possibility that the infection is viral and therefore would not respond to this treatment. Even when a viral infection can be confirmed, this may not rule out a bacterial co-infection and AM drugs may still be prescribed. In such instances, a diagnostic device that could rapidly confirm a viral infection with the same speed and accuracy as, e.g., a strep test, would be financially beneficial and avoid unnecessary prescribing of AM drugs. The device would also give patients who have a viral infection an explanation as to why they are not getting the AM drug they may want.

Another area where rapid diagnostics would be helpful is for identifying gram-negative bacteria and sepsis. We heard during our 2018 interviews that there are no good rapid diagnostics available for use in emergency settings. Rapid diagnostics are also needed to accurately determine the source of an infection. Lastly, doctors expressed interest in a (theoretical) diagnostic that could, within 12 hours, provide results on what organism is causing the infection and what treatments the organism is sensitive to, given the substantial length of time now needed for antibiotic susceptibility testing. The ability to rapidly diagnose the source of the infection in clinical practice is also important given the potential participation of these practices in CTNs.

In addition, AM drug research and development is long and expensive, and it can take 10 to 15 years from initial discovery before the drug is commercially available (Blaskovitch, 2017). Funding clinical trials is challenging, as small-and medium-sized enterprises (SMEs) struggle to raise the capital to run these trials and large corporations have exited the market (Renwick & Mossialos, 2018). Further, only a small percentage of AM drugs in development are ever approved so, as for many other drugs, the effort and expense of developing most of these early AM drug candidates makes investment in these companies high risk. Interestingly, however, the calculated success rates to bring a drug from IND to FDA approval for AM drugs approved from 2011 to 2020 was 16.3 percent, more than twice the overall pharmaceutical industry success rate of 7.9 percent (Thomas & Wessel, 2022). New AM drugs with novel targets also had a high success rate (13 percent) (Thomas & Wessel, 2022). These rates are much higher than the success rates for

oncology drugs, which average 5 percent, but comparatively receive much greater investment (Thomas & Wessel, 2022). The data show that there are more significant factors than just the scientific challenges that result in the suboptimal level of AM drug development activity.

4.3.2 Economic Challenges

There is a strong consensus in the literature and among experts that the most formidable challenge to AM drug development is that returns for AM drugs are lower than those for other biopharmaceuticals. That is, too few AM drugs are in development because developers are disincentivized by relatively lower anticipated returns on their investments in those products. Hence, they are more likely to focus their development efforts on products with relatively higher anticipated returns. Experts we consulted noted that push incentives have resulted in development of more AM drugs, but the revenue generated from most antibiotics after product launch is not sufficient compared to the cost of development and that of more profitable drugs. Returns on AM drugs are limited due to short duration of treatment, small patient populations, and AM drug stewardship (Renwick & Mossialos, 2018).

The majority of bacterial infections can be treated with currently available, low-cost generic AM drugs (Blaskovich, et al., 2017). Drugs for chronic conditions, such as those used for high cholesterol levels, which are taken continuously for years by millions of people, are much more profitable than AM drugs (Blaskovich, et al., 2017). In addition to the short duration of treatment, the patient population with MDROs is small. The volume of AM drugs is also affected by potentially depressed prescribing due to DRGs and AM drug stewardship, compared to chronic disease treatment.

Based on our conversations with drug developers in 2018, novel AM drugs rarely have revenues greater than $50 million per year, making it difficult to achieve profitability within a time frame acceptable to investors. AM drugs designed to treat resistant infections do not cost more than a few thousands of dollars for a course of treatment, whereas anticancer therapies can cost over $100,000 per year (Blaskovich, et al., 2017).

The lack of high volume sales of AM drugs and their typically low price per unit depress revenues in this drug category. Based on our 2018 interviews, success in the AM space used to be defined as a return on investment of six to nine times the original investment over nine to 10 years, but today companies barely get a return of two or three times their original investment over the same time period. In 2018, drug developers we interviewed told us that venture capital firms typically only invest in projects expected to return five to 10 times the initial investment within four years, but that such rates of return are simply not feasible for many AM drug development programs. Hence, investors we interviewed in 2018 indicated that they are drawn to projects with a higher probability of a short-term return, such as oncology and orphan drugs. Orphan drugs are drugs that are used to treat rare diseases. These drugs are of interest to pharmaceutical investors because they can often command high prices and have fewer competitors in the market, leading to higher profits for the companies that produce them. Additionally, the developers of orphan drugs are often eligible for special incentives and support from regulatory agencies, which can make orphan drugs more attractive investment opportunities.

Since new AM drugs are limited in use, due to stewardship and the small patient populations with multidrug-resistant infections, sales of new AM drugs are typically low. The constantly evolving nature of AMR in bacterial pathogens also presents a challenge because of the possibility that by the time the drug makes it to market, the demand for the product may have waned. Getting new, more expensive AM drugs onto hospital formularies is difficult when a cheaper alternative that treats the majority of infections exists. However, some of the older AM

drugs are associated with significant side effects. For example, polymyxins, the antibiotic often chosen to treat highly resistant Gram-negative bacteria, can cause renal toxicity.

The DRG system also incentivizes the use of cheaper AM drugs. Medicare reimburses hospitals through the DRG system in a bundled payment, so hospitals are reimbursed a fixed amount for certain diagnostic categories and conditions, which incentivizes their use of the cheapest available therapeutics, regardless of potential side effects. Many private insurers follow Medicare's billing rules and thus it has been challenging for hospitals to receive coverage for newer, more expensive AM drugs. Many AM drugs also have generic versions, which have lowered prices significantly (Shlaes, 2020).

Further, the current number of AMR cases in the U.S. is much lower than other diseases, resulting in lower demand. Some studies have even shown encouraging results that AMR is stable or decreasing for some pathogens in the U.S. and is not as significant as thought elsewhere for some of the major MDRO infections (Jernigan, 2020; Diallo, 2020; Abat, et al., 2018). Part of the challenge is that the burden of AMR is often estimated by mathematical models, which are sometimes based on hypothetical estimates rather than actual counts of cases or are based on data from areas where cases are high. Studies indicate that higher quality data are needed to estimate the burden of AMR-attributable mortality and morbidity (Diallo, 2020; Pezzani, et al., 2021). Most of the doctors we spoke to in 2018 reported seeing drug-resistant infections infrequently in the U.S. Some institutions have had different experiences related to resistance that in many cases can be attributed to the institutions' locations and specific practices. In rural settings, where AM drug use is limited, and the hospital may be far away from densely populated areas, there is less resistance. According to one doctor in an urban setting, multi-drug-resistant gram-negative bacteria have become common and treating them is part of the standard of care; local doctors therefore have more experience dealing with the new reality and have various options for treatment depending on the infection. Also, the number of drug resistant infections is much higher in low- and middle-income countries at present, but these can also pose a future global threat. For example, bacteria carrying the NDM-1 resistance gene spread across the world from its origin in India (Cama, et al., 2021). In general, , according to experts interviewed for this report, drug resistant bacterial infections are much less transmissible than a virus like COVID-19, so AMR appears more sporadically.

Given the above economic conditions, many large pharmaceutical companies have abandoned the AM drug market (Shlaes, 2020). Several large companies have shut down their antibiotic research projects in recent years, including Novartis, AstraZeneca, Sanofi, and Allergan (Megget, 2018). At present, small biopharmaceutical companies are doing most of the groundwork of AM drug discovery, but partnerships with traditional large biopharmaceutical companies are usually needed to fund the expensive late stage clinical trials needed to gain approval or to conduct the marketing campaign once an AM drug is approved (Blaskovich, et al., 2017). Over 95 percent of the drugs in development today are being developed by small companies and 70 percent of them have never developed, commercialized, and marketed a product before (Pew Trusts, 2021). Private funding is being replaced by public funding. The National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA) support preclinical and clinical trials (National Academies of Sciences, Engineering, and Medicine, 2022). When large pharmaceutical companies exited the AM drug market, such as Novartis, Allergan, and The Medicines Company, venture capitalists funds that may have at one time invested in AM drugs viewed these companies' departures as evidence that there was little money to be made in the AM space, and so even fewer potential AM drug investors exist today. Stock prices also indicate how investors perceive the likelihood that a company will be profitable in the future. Today's perception of the AM development space is reflected in the stock prices of the AM drug

development companies, such as Spero Therapeutics, Nabriva, Iterum, and Paratek, which are at all-time lows.

There also are examples of companies that have filed for bankruptcy after bringing a product to market, such as Achaogen (manufacturer of Plazomicin) and Melinta (manufacturer of four FDA-approved antibiotics). These bankruptcies are also likely dissuading venture capital and retail investors from investing in AM drugs. However, these failures are not necessarily unique to the AM drug market and may be due to the drug itself (e.g., no or minimal added clinical benefit) or company management. Some observers claim that recent bankruptcies by pharmaceutical companies that gained FDA approval for novel AM drugs show that the current pharmaceutical market model does not work well for AM drugs (Klug, et al., 2021). However, other factors may also have contributed to company failures. For example, Achaogen's Plazomicin demonstrated limited clinical benefit over existing treatments for its approved indication (treating drug-resistant urinary tract infections) and was not approved by FDA for a second indication (treating drug-resistant bloodstream infections caused by Carbapenem-resistant Enterobacterales (CRE)). The inability to obtain FDA approval for a second indication may have contributed to meager sales and Achaogen's ultimate bankruptcy (Aagaard, et al., 2021).[11] Cubist Pharmaceutical's product Cubicin, in contrast, was considered a blockbuster drug, for the treatment of MRSA, with more than $700 million in sales in nine months (O'Brien & Chu, 2020). However, the U.S. Court of Appeals invalidated several Cubicin patents resulting in early generic development that ultimately led to erosion of those sales (O'Brien & Chu, 2020). For our 2018 study, both early stage investors and drug developers described commercialization challenges that face new AM drugs, which we also described earlier.

An underlying issue that emerged during our 2018 study – and that has potentially contributed to the lack of investment— is society's perception of AM drugs. Today, people apparently do not value AM drugs as much as, e.g., cancer drugs. Experts noted that people are willing to pay a lot of money for a cancer drug that may give the patient a few more months to live, while AM drugs that could save lives are not valued similarly. Society takes for granted that AM drugs cure bacterial infections at a low cost. Reframing how society values AM drugs and their development could increase the probability of successfully replenishing the AM drug pipeline.

4.3.3 Regulatory Challenges

Regulatory challenges facing the market largely consist of clinical trial requirements and reimbursement. Partly due to post-marketing failures that showed safety issues with some approved AM drugs (such as with telithromycin), clinical trial designs required for AM new drug applications (NDAs) have gotten more complex, requiring larger pools of patients and somewhat restrictive eligibility criteria. This has increased the cost of conducting such trials, making AM drug investment less attractive (Spellberg, 2014; Renwick & Mossialos, 2018).

As noted previously, Medicare reimbursements for AM drugs are based on DRGs, which encourage use of lower cost and older AM drugs. Hospitals that require branded AM drugs to treat drug-resistant infections therefore would lose thousands of dollars on each patient requiring such treatment, disincentivizing the addition of new AM drugs to their formularies (Klug, et al., 2021). Some reforms in the reimbursement mechanisms on novel AM drugs, New Technology Add-on Payments (NTAPs), were made by the Centers for Medicare and Medicaid Services (CMS) in 2019 to encourage innovation in the field. CMS revised the rules for these payments so that more AM drugs would qualify for the program (Shaw, 2021). The goal of these payments is to allow access to drugs that show substantial improvement over existing drugs but whose cost are more than allowed

[11] This means that the clinical evidence submitted in support of the second indication was insufficient/inconclusive for FDA approval.

under DRG reimbursement. NTAP is temporary, however, lasting only three years, and in some cases just two. It is intended to help with adoption of new AM drugs until the DRG adjusts for their use (Rex, 2019). Furthermore, CMS has been challenging AM drug developers to meet the criteria for an NTAP payment given that the traditional non-inferiority clinical trial design cannot demonstrate that the new drug is superior to existing treatments (because placebos cannot be used) (Verma, 2019).

Some improvements have been made recently that may have increased use of NTAP. The FY2020 Inpatient Prospective Payment System Rule included changes that specified that for Qualified Infectious Disease Products (QIDP), substantial clinical improvement in outcomes for a specified patient population compared to current treatments does not need to be shown, and the NTAP payment was increased from 50 percent to 75 percent (Verma, 2019). QIDP is a designation granted by FDA that is available to AM drug developers to expedite approval of innovative drugs that target drug-resistant infections (Verma, 2019).

4.4 EXPERT PERSPECTIVES

We interviewed the experts listed in Table 1 to explore the inefficiencies in the AM drug market not uncovered during our previous research, as well as possible interventions that could address these issues. We organized the results from these interviews by topic, based on the questions asked (see Appendix A for the interview guide). While many of the experts repeated some of the points made earlier, the interviews also revealed some new and useful information, summarized in Table 3 at the end of this section. The statements below consist of opinions expressed by experts, cited using the codes provided in Table 1, or otherwise cited from literature.

4.4.1 Challenges Specific to the U.S. AM Market and Potential Government Interventions

One of the objectives of this study is to uncover issues that pose a challenge for the U.S. AM drug market but are less commonly discussed. We therefore asked experts to share what challenges the U.S. AM drug market faces in addition to those presented earlier, as well as possible government interventions that could address these challenges.

As noted previously, part of the reason for the struggle to bring novel AM drugs to market is that the science is very difficult (A1). However, this is not unique to the U.S. AM drug market and occurs in other pharmaceutical markets as well (e.g., medications for Alzheimer's). Some experts feel that the focus should be on market mechanisms – for example, the best reimbursed diseases often have the best research (BC1). The AM drug market is different than other drug markets in one important regard – bacteria develop resistance over time to existing drugs. This renders existing drugs less and less effective over time and raises concern about the availability of effective treatments in the future. This concern is what drives the discussion about the need for novel AM drugs (D'Andrea, et al., 2019).

Two strategies preserve the availability of effective AM drugs – stewardship of existing AM drugs to preserve their effectiveness, and the production of novel AM drugs. At the same time, the industry is struggling to bring high quality, novel AM drugs to market (Hyun, 2022). Understanding the challenges that face the U.S. AM market will be helpful in identifying potential interventions which could address how to ensure effective drugs continue to be available to treat drug-resistant infections. The challenges faced by the U.S. AM market that were most frequently identified during our expert interviews include:

- The structure of the current U.S. pharmaceutical business model.
- The quality of new AM drugs.

- The relatively low number of cases of drug-resistant infections in the U.S.
- The threat of an increase in AMR.

We discuss each of these in detail below, followed by interventions suggested by the experts.

4.4.1.1 Structure of the Current U.S. Pharmaceutical Business Model Challenge

Many of the experts discussed a challenge faced by the U.S. AM drug market that is commonly reported in the literature as well, namely that the current pharmaceutical business model is problematic for AM development (A1, A2, BC1, BC2, BC3, P1, P2, O4). Under the current model, investors provide capital for companies to develop new products and the revenue from these products, consisting of volume and price per unit sold, provide returns on those investments. While there is a great deal of innovation, companies are set up to answer to shareholders rather than the needs of the general public, and AM drugs do not generate enough revenue to justify investment (A4). While there is a profit to be made, the returns to AM drug development are insufficient for large companies to maintain AM drugs as part of their portfolio when compared to the returns from other therapeutic areas, such as oncology and immune therapies (A1). In other industries, the profits that AM drugs generate would be considered sufficient, but in drug development, the perception is that the returns should be higher, since prices are set much higher for other drugs (O4, O5). Furthermore, the market is based on driving sales volume, which leads to AM drug overuse (A1).

The traditional approach to pharmaceuticals, the blockbuster drug model, does not incentivize companies to produce novel classes of AM drugs (O4). From the perspective of the biopharmaceutical companies interviewed, the annual revenue from AM drugs is insufficient and the main challenge facing the AM drug market. They noted that short courses of drug treatment, low prices, small populations with the disease state, and stewardship measures are the main factors that result in low returns and subsequently fail to attract investment to the space (BC1, BC2, BC3). Other experts interviewed also noted the low reimbursement rates for these drugs (O3, O2). Any of these factors, except stewardship, can be applicable to other drug markets, but for AM drugs, all are typically present. While biopharmaceutical companies note that the lack of sales volume in AM drugs, combined with stewardship, does not yield sufficient market returns, it should be noted that companies do not always fail due to the lack of adequate market returns. They also fail because the drugs are not as good as those already available; other times, the company fails because of poor decision-making (O2).

AM drug stewardship and low pricing of AM drugs currently in use, relative to new AM drugs, can result in doctors prescribing older generic drugs.[12] Physicians may also not be well informed about the newer drugs and how to use them, resulting in the use of older treatments (O2). New AM drugs are often third or fourth treatment options and used only when older treatments fail. Further, the first-line treatments typically are effective in treating almost all infections, negating the need for the newer treatments (O2). Also, in the last two decades, the number of products that have been withdrawn from the AM drug space is three to four times higher than other classes, likely due to no or minimal added clinical benefit and high pricing (O4).

Companies have much more lucrative options, such as the oncology market (P1, P2). The pipelines reflect this investment, as oncology currently has more than 1,700 products in the clinical pipeline versus 250+ in the AM drugs pipeline (P1, P2). It is, however, not clear why oncology

[12] Stewardship does not result in the selection of lower-priced drugs per se. New AM drugs are "in reserve" and higher priced; older generic AM drugs are first-line and lower priced.

should serve as the yardstick for comparison. One expert noted that the supranormal pharmaceutical prices for other drug classes, such as oncology and Hepatitis C, contribute to the problem with AM development, as this pricing draws investors to other drug classes (O4).

AM drugs that are effective and first-in-class can do well and command a higher price (O4). Some AM drugs can be successful in the market if the treatment population is large enough or the course of treatment is long enough (BC1) as discussed further below. The orphan drug designation also exists for rare diseases, which includes some bacterial infections. While the orphan drug designation has played a role in getting some AM drugs on the market, experts do not consider it sufficient to address the problems in the market as stewardship and historically low pricing of antibiotics have impeded its use (BC1, BC3). Rare bacterial infections are different from other rare diseases since antibiotic treatments are subject to stewardship, clinical trials typically show non-inferiority rather than superiority, and cheaper existing treatments are frequently available to treat the infections (although these may have undesirable side effects). These factors reduce the likelihood of using the AM drug. Barriers also exist because the payer has to reimburse the cost of the product and, as noted earlier, AM drugs are historically priced much lower than designated orphan drugs (BC1).

Proposed Interventions

Remove AM drugs from the DRG reimbursement system. Removing AM drugs from the DRG reimbursement system is theoretically a solution to the low pricing of new AM drugs (BC1). This measure was also suggested by experts interviewed for our (2018) study as well, as it gives hospitals the ability to be reimbursed for the higher price of novel AM drugs, which in turn would lead to higher returns for developers. Those interviewees noted that changing AM pricing and reimbursement schemes would lead to more robust returns and would also stimulate investor activity. An example was given by a venture capitalist who explained that oral AM drugs can be given in an outpatient setting where they are not subject to DRG pricing, thus improving their commercial success. In practice, however, even with such changes, those administering the drugs are not incentivized to use the drug due to stewardship and the lack of sales volume will affect the ability to generate a sufficient market return (BC1). First-line AM drugs are also generally effective (although toxicity is an issue for some) and low prices/lack of volume do not justify investment in developing additional treatments (BC3, O3).

Change to a market model that delinks sales from volume of drugs sold. The return from antibiotics is currently directly proportional to the volume of products sold and the volume is too low to provide adequate returns for developers. Two of the biopharmaceutical companies interviewed therefore suggested decoupling sales from the volume of drugs sold, noting that the list of resistant pathogens is known, as is the return needed to justify investment.[13] They suggested two possible pull incentives: the subscription model and pediatric priority review vouchers, likely because drugs for rare pediatric diseases command significant revenue. They noted that these would offer the return companies seek as an incentive (Meyer, 2021). The subscription model pays a flat price to a company annually for a guaranteed supply of a new antibiotic. A pediatric priority review voucher provides rights to a faster FDA review and can be transferred to another drug sponsor (BC1, BC2). Priority review vouchers are very valuable to companies because getting a new product to market earlier can allow the company to earn more from the drug and possibly launch a product before competitive products enter the market. Other experts suggested the option of awarding a monetary prize upon regulatory approval of novel AM drugs that are needed to address MDROs (P1, P2). This would address the unworkable business model issue since AM

[13] Although the list of pathogens is known, this list is not static, and it should be noted that new pathogens can emerge at any time.

drugs function more like public goods (A2). Another expert suggested passage of the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act, which includes a subscription-style model that would offer installment payments to AM drug developers upon approval (O1) (also see Section 4.4.3.2 below).

Subsidize post-market activities. Experts also recommended changes that could reduce costs incurred by companies and therefore increase their likelihood of survival after regulatory approval. For example, the government could alleviate costs incurred by companies once the drug is on the market by subsidizing post-market activities (O2). For small companies, post-market pediatric studies are very expensive. Supporting pediatric studies and/or manufacturing might be helpful to keep companies financially viable and operational (O3).

Form a public entity or public-private partnership for AM drug development and commercialization. Some experts thought it might be worth exploring different models for AM drug development and commercialization. One expert suggested the formation of new entity, maybe a PPP, which manages the AM drug portfolio, including new drugs (BC2). Similarly, another expert thought that encouraging consolidation of development and commercialization efforts (although not necessarily under one entity), if possible, would help to centralize and maintain knowledge and manufacturing of AM drugs that could address future AMR (O3). Developed products could be "parked" (without commercialization). Government could help ensure that the manufacturing capacity is available when these products are needed (O3) (also see Section 4.4.4.2 below).

4.4.1.2 Quality of Clinical Evidence for New AM Drugs

Challenge

Several experts noted that there should be a greater focus on drug quality rather than drug quantity with respect to AM drug development. A (2016) study by Deak et al. found that AM drugs launched during the 2010-2015 period had been approved without any clinical superiority over older drugs and yet were priced higher. A number of experts noted that the quality of the clinical evidence for new AM drugs needs to be improved (A2, A5).. The market is focused on pathogens, rather than patient outcomes (A2). Only one pivotal trial is required, the study populations are small, and the drugs are not tested on the patients who need them most – those who are older, sicker, and have drug-resistant infections (A2, A5). New treatments for drug-resistant infections are often supported by clinical trials that include patients with infections caused by non-drug resistant infections (Yahav, et al., 2020). Combined with the non-inferiority design of the clinical trials and the relatively higher prices of new AM drugs, excluding the patients that need these products most makes it difficult for physicians to decide to use these new drugs (A2). In addition, post-marketing efficacy data are typically insufficient to overcome this problem (A2). Physicians may not use new AM drugs because they do not know whether they are better and are reliant on post-market data to make this determination, which is often delayed and also of poor quality (A2).

Proposed Interventions

Test for superiority rather than non-inferiority. One expert suggested that clinical trials should test for superiority and not non-inferiority and the government should set high standards for clinical evidence (A2). Non-inferiority trials seek to determine whether the new antibiotic is no worse than existing treatment. These clinical trials also typically exclude older and sicker patients (A2, A5). In contrast, a superiority trial would show that the AM drug is better than those currently on the market (A2). Superiority trials do not need to be large and if populations with drug resistant infections are difficult to find, clinical trial infrastructure investment in locations where resistant infections are prevalent can be made, such as the MDRO Network, or the study can be conducted at multiple sites (Powers, et al., 2018).

Focus on patient outcomes. According to one expert, elderly patients should be added to the study populations, as the effectiveness of AM drugs is not just about killing the pathogen, but also about the host's immune response (A2). The government should subsidize drug research to develop drugs that improve outcomes for infections that are drug resistant as well as those that are not drug resistant (A2). Many infections result in death because of the host's immune response to the pathogen and many could benefit from interventions with host immune modifiers (A2).

Develop new platforms for discovering AM drugs. For example, Northeastern University developed a novel platform called iChip to discover AM drugs in the soil that will not grow under the artificial conditions of a laboratory (Singer, 2022).

Use clinical trial platforms. Clinical trial platforms, which compare multiple interventions against a single control group, could be used to generate higher quality clinical evidence on new AM drugs (A2, BC1, O4).

Educate physicians on AM drugs. Most physicians are not well-informed about AM drugs and how to use them (O2). Physicians also cannot make decisions based on poor quality data (A2). If they are provided with higher quality evidence and better AM drugs, they might be more inclined to use them.

4.4.1.3 U.S. Market Size for Drug-resistant Infections

Challenge

Experts interviewed noted the lack of urgent need for new AM drugs in the U.S. The U.S. does not need new AM drugs as much as other countries because the AMR rate is relatively low (O3, O2). One expert noted that the U.S. AM drug market is small and is expected to shrink further as U.S. AM drug stewardship increases (O1). The market outside the U.S. is much larger but is difficult to access for small companies who are currently developing AM drugs (O2).

An expert in tuberculosis (TB) also noted that the main challenge for the U.S. market is that there are not enough cases of drug-resistant infections in the U.S. to comprise a profitable market. While numerous cases of drug-resistant infections occur elsewhere in the world, much lower drug prices in these areas mean that potential profits are not great enough to incent a large company to develop these drugs (F1).

While there is the potential of a future problem with resistance that needs to be addressed, it is not known how large a problem this will be, which creates uncertainty and risk for companies. For example, the rise in methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) has not been as significant as had been expected (Jernigan, 2020). The challenge is that there is insufficient need today, but there could be a potential problem in the future, but the details of this potential problem are difficult to predict (O3).

Proposed Interventions

One possible intervention to address the issues related to U.S. market size is to segment the market into drugs that can be made for profit and those that will not earn a profit, which includes many AM drugs. Once it is ascertained that some AM drugs cannot generate the kind of profit desired by private companies, it changes the business model to a not-for-profit model. This further implies that the drug cannot be provided through private markets and that at least some degree of public funding is necessary (F1). With TB, a successful new drug cocktail was brought to market through a partnership with a non-profit organization, the TB Alliance (see also Section 4.4.4.2 below). The 2022 National Academies report on combating AMR also suggested it might be possible that drugs with a very small market might be natural non-profits (i.e., it is not possible to profit from their sale) and an alternative might be to invest in a non-profit drug development

institute (National Academies of Sciences, Engineering, and Medicine, 2022). Another suggested intervention would be to help companies to access foreign markets (O2). If companies are able to sell their products to a few hospitals in Southeast and East Asia, they could increase their returns (O2).

4.4.1.4 Threat of Increase in AMR

Challenge

The potential for AMR to become a significant problem in the U.S. is a constant threat and needs continued attention. Overuse of commonly used antibiotics is a major challenge because the market in the U.S. is currently structured as a fee-for-service model and does not account for the social cost of AMR (A1). This leads practitioners to overprescribe as they get paid per prescription dispensed, which exacerbates AMR (A1). That said, there are many different opinions about AMR. One expert noted that a current increase in AMR could become a bigger issue over time, which was also discussed in a recent CDC report (O1) (CDC, 2022). Another expert has seen evidence that AMR is increasing and might have been accelerated by COVID-19 when many patients were needlessly given AM drugs (O1).

Experts also pointed out that there are not many innovative drugs expected to come into the market in the next five years, based on the clinical pipeline (although in 6 to 10 years, more innovation might be seen due to the work by Global Antibiotic Research and Development Partnership [GARDP] and CARB-X)(O1). This makes it even more important to address AMR. Experts also noted that you cannot predict the future and the resistance of some pathogens, e.g., the resistance of CRE/MRSA has not grown as previously projected (O2). Another expert emphasized that much of the current narrative and proposed solutions regarding AMR are based on expert opinion, while concrete evidence about the level of AMR and the effectiveness of drugs are also available (A2). As noted earlier, reductions have been seen in the resistance of some pathogens, which suggest prevention and stewardship efforts are having some success (Jernigan, 2020). Overall, the uncertainty about AMR is very challenging for the market because AMR is continually evolving, and it is difficult to predict its evolution (A2).

Proposed Interventions

Some recommendations to combat the continuing threat of AMR include greater oversight of stewardship programs to ensure effectiveness and limit the spread of resistance (A2). One expert also raised the importance of addressing the issue of AM drugs in agriculture and in the food chain to reduce AMR (A3). Another suggested improvements in hygiene and cleaning, which can prevent infections and reduce the occasions when AM drugs are necessary (A1). Research could also be funded through NIH to identify strategies to reduce infections and therefore AMR (A1). Prescribers should also be properly incentivized to implement stewardship (A1). Insurance companies can also help reduce overprescribing by analyzing data on medical claims and pharmacy data (A1). CMS could play a role as well, given that healthcare facilities and Medicare and Medicaid are under their purview (A1).

Another expert suggested that, to move away from AMR, we need to rely less on AM drugs and more on anti-virulent approaches (BC2). Anti-virulent drugs interrupt the process of infection in the host by depriving the pathogens of their virulence factors, disarming but not killing the pathogens (Martinez, et al., 2019). Anti-virulent drugs have the potential to avoid or minimize resistance development as the pathogen is not being killed (Totsika, 2016). Research on anti-virulence, including gene editing and gene silencing, is therefore very important to reduce the prevalence AMR and should be supported (BC2).

Appropriate use of innovative diagnostics could also help address AMR. In Norway, physicians are able to use narrow spectrum AM drugs by applying rapid diagnostics (O1). In Sweden, a company called 1928 identifies bacterial species from DNA sequences that are uploaded by hospitals to the Internet (1928, Undated). Whole genome sequencing data enable fast and accurate pathogen identification. The system also identifies the drug needed to treat that pathogen. In the event of an AMR epidemic, rapid diagnostic testing will also be a priority, similar to the need for rapid tests for the SARS CoV-2 virus in the current pandemic (Cama, et al., 2021). In the U.S., barriers to using diagnostics are due to costs, combined with a lack of uptake by providers and appropriate rapid diagnostics (Trevas, et al., 2021). Data are needed to demonstrate clinical benefits and reimbursement practices need to be revised to reflect the value of the test to the healthcare system and public health (Trevas, et al., 2021). Incentives are also needed to develop rapid diagnostic point of care tests (Trevas, et al., 2021). Product development partnerships could also be used to support the development of diagnostics (O4). Because companies do not have an incentive to invest in AMR prevention activities, it is important for the government to invest in this work (A1).

Some experts also noted that a new group should also be used for tracking AMR. The CDC maintains an antibiotic resistance threat list, and the WHO publishes a global priority pathogens list. These are often used to identify pathogens of concern, even though a key pathogen (Tuberculosis) is excluded from the WHO list (which comprises the most cases around the world) (A4). Building the world's capacity for surveillance is essential to ensure that AMR can be identified and addressed in a timely manner (BC2).

4.4.2 Topics Related to AM Drug Development – Scientific Issues

Novel AM drugs could provide alternative treatments for drug-resistant infections. The 2020 WHO report on the global preclinical pipeline for AM drugs lists 292 preclinical candidates across many new modalities (vaccines, AM peptides, bacteriophages, virulence inhibitors, immunomodulatory compounds) (WHO, 2021). In addition, combinations of existing AM drugs that may have synergistic activity might be promising (Coates, 2019). We asked experts to comment on current innovation in AM drug markets and the role of innovation in addressing the problem of AMR and how it can be encouraged.

4.4.2.1 The Promise of Innovation

Innovation plays a significant role in fighting drug-resistant infections. For example, in 2019, the FDA approved a new drug, Pretomanid which was developed by a non-profit organization, the TB Alliance, as part of an oral cocktail of products (BPaL) developed for TB (F1). This is one of the successful examples of experimentation with a combination of existing AM drugs (along with a newly developed drug by a non-profit organization). Phage lysins are another promising new technology. Although high-risk, if they can be shown to be a superior treatment, phage lysins may be used to treat patients with life-threatening infections (O3) (Anon., 2022). Furthermore, some bacteremia patients also require a longer period of treatment, which would be appealing to investors.

Innovation in approaches to discovering new AM drugs is also very important and can be supported by product development partnerships (O4). An example is the previously mentioned iChip that continues to discover new microorganisms and in 2015 led to the discovery of teixobactin, a novel AM drug that kills pathogens and is more robust against resistance (Martin, 2015).

4.4.2.2 Limitations of Innovation

Many experts commented, however, that innovation can only partially address AMR. As discussed previously, AMR must also be reduced through prevention, infection control, and stewardship simultaneously (A1, A2, A2, BC1). Even though there is a high level of innovation in the AM space at present, AMR can overwhelm any new innovations (A2). Moreover, the regulatory requirements for innovative products will likely be more onerous than for traditional AM drugs (A2). Alternative technologies like anti-virulent drugs and phages are promising, but many questions remain with respect to regulatory approval, manufacturing, and intellectual property rights. During our 2022 interviews, some experts also indicated that they think these questions will likely be answered in the near future (O1). Regardless, these new technologies are high-risk investments, and most will not make it to market (O3).

Any novel AM drug will also be subject to the same market model as traditional AM drugs (BC1). While both the preclinical pipeline and clinical pipeline are relatively robust (O2), the prospects of these drugs being commercially successful is dim. As noted previously, this could potentially be solved if the small biopharmaceutical firms had access to the foreign markets with their higher incidence of drug-resistant cases (O2). While the payments for antibiotics in foreign markets will be lower, these could be offset by the larger volume of patients in these markets.

4.4.2.3 Role of Government in Innovation

Investors want high returns from drugs that can be developed quickly, which is at odds with the need for better, novel AM drugs, which require much longer to develop (A2). Government can play a role to alleviate the uncertainty and risk associated with AM drug development (A2). For example, government could fund CTNs and participate in private-public partnerships. Innovation can also be encouraged by understanding where gaps of funding exist (A1). Many experts commented, however, that much is already being done by BARDA, CARB-X, and the Wellcome Trust to encourage innovation (A2, O2, O3, BC1, BC2, BC3).

4.4.2.4 Clinical Trial Networks (CTNs) and Innovation

One option to encourage innovation might be to encourage use of a clinical trial network (CTN), like the European Clinical Research Alliance on Infectious Diseases (ECRAID). With the traditional approach, a clinical trial needs to be set up each time a new AM drug is tested, an inefficient process that requires recruiting and enrolling at dozens or even hundreds of sites (McDonnell, 2016). This can make clinical trials too expensive for some drug developers with a promising drug candidate (O5) but that lack the resources to engage a clinical research organization (CRO) or to conduct trials themselves. A CTN allows a drug developer to quickly plug into the existing network (McDonnell, 2016). A CTN for AM drugs would need to be government-funded, possibly as a public-private partnerships, as clinical trial research organizations are neither equipped nor incentivized to develop these (O5) (McDonnell, 2016). Furthermore, the CTN would need to study drugs for an infection that is common enough for the network to be productive (O5). Input from infectious disease physicians from all healthcare settings, including academia and the National Institutes of Health (NIH), will be essential for success (O5).

Government-funded CTNs could spur innovation, as they did during the COVID-19 pandemic (O5). If AM drug developers are provided easy access to CTNs, it will lower their clinical research costs and enable them to test their product (O5). CTNs can also be used to develop drugs for rare infections, trials for which can take years to recruit and enroll patients. Using existing CTNs that are focused on more common diseases will allow more efficient and economical evaluation of drugs for rare infections (O5). While there will be challenges to overcome to ensure the CTN is productive, CTNs might result in innovative and better products entering the market, as it may

encourage companies to enter many of their product candidates that may be sitting in freezers into the clinical research phase (O5).

4.4.2.5 Other Considerations to Encourage Innovation

Any innovative effort will require a profile of targets. The WHO determines whether new AM drugs are innovative based on whether the drug meets four criteria (new chemical class, new target, new mode of action, and absence of known cross-resistance) (WHO, 2021). These criteria are very restrictive, however, requiring a new class of drug/new target and do not put any weight on a change in dosage form or toxicity (P1, P2). As discussed above, experts noted that non-inferiority trials, which only show that the new drug is no worse than an existing drug, make it challenging to bring AM drugs to market. Non-inferiority trials do not make it likely that physicians will want to use a new, innovative drug over one that they currently use unless there is some significant clinical benefit to doing so, such as significantly reduced side effects (A1, O1). Expansion of dosage forms (from injectable to oral, for example) and a reduction in toxicity are therefore worthwhile pursuits (P1, P2).

In general, FDA has been supportive and flexible with clinical trial requirements for AM drugs (O3). FDA interaction, especially early in drug development, and transparency are also helpful to encourage preclinical pipeline candidates to advance to IND-ready candidates (A1, O2). Given the importance of discovery, it is also essential that the talent pool is grown and encouraged since experts in this area are being lost through retirement (O1).

4.4.3 Topics Related to AM Drug Development – Economic Issues

4.4.3.1 Need for Large Pharma Investment

Large biopharmaceutical companies have withdrawn from direct investment in AM drug development in recent years, although they are still investing indirectly (e.g., the AMR Action Fund, which was established in 2020 and is funded by large pharmaceutical companies to support AM drug development and encourage the development of innovative antibiotics). We asked experts to comment on the continued interest of large firms in the AM drug market.

Most experts agree that large biopharmaceutical companies think that profit prospects for the AM drug market are too bleak to be at the core of their business models (F1). Biopharmaceutical companies have obligations to shareholders to make lucrative investments; therefore, it is economically rational that they have exited the AM drug market (BC1, BC2, BC3). Many large companies have also largely left the basic and translational fields of pharmaceutical science in general and become purchasers of small companies with promising drugs in development (A2).

Many of the large companies also see reputational value in supporting organizations like the AMR Action Fund and recognize the threat of AMR (A1, A2, BC1, BC2, BC3, O3, O2). There is some pressure on these companies to be part of the solution and they still have hope for profitability as well (O1). By engaging in and contributing to these types of funds, they receive positive press, but do not have to invest much (A2, P1, P2). Phage development is already being supported by the AMR Fund (O4). Phages are a type of virus that infect and kill bacteria without negative effects on the human cells (Principi, et al., 2019). On April 4, 2022, the AMR Fund announced that it had invested in the work by two companies, Adaptive Phage Therapeutics and Venatorx Pharmaceuticals (AMR Action Fund, 2022).

It is important for large companies to continue to play a role in the marketplace and additional pathways are needed to get them involved (F1, P1, P2). The discussion about pull incentives and the potential size of these awards have resulted in continued interest by large companies in this space (A2, O4). With the subscription model, the U.K. is hoping to re-engage

large companies in the AM space as well (P1, P2). As found in our earlier research, when large pharmaceutical companies, such as Novartis, Allergan, and The Medicines Company, exit the AM drug market, , venture capital funds that may have at one time been interested in investing in AM drugs view these companies' departures as further evidence that there is no money to be made in the AM space, and so even fewer potential AM drug investors exist today. Delinked payment models might bring large companies back into AM development (P1, P2).

4.4.3.2 Financial Incentives to Encourage Investment in AM Drug Development

A recently published report by the National Academies of Sciences, Engineering, and Medicine (NASEM) on combating AMR provides an extensive overview and evaluation of the push and pull incentive programs available that support the development of AM drugs (National Academies of Sciences, Engineering and Medicine, 2022). Thus, we do not discuss these in detail here. Instead, we provide a brief overview of select push incentives for context, and focus primarily on pull incentives, including transferable vouchers, subscription models, market entry rewards (MERs), reimbursement changes, and high-volume purchases of AM drugs for the National Strategic Stockpile.

Push Incentives

The National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA) offer multiple grants and awards to support research and development of new AM drugs in the United States. In Europe, the Joint Programming Initiative on Antimicrobial Resistance provides similar funding. Private foundations, such as the Wellcome Trust and the Bill & Melinda Gates Foundation, also support the development of new AM drugs either individually or through public-private partnerships (PPPs), like the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). Many of these programs fund early discovery, but the boundaries are not always clear. NIH grants can provide funding up to regulatory approval. BARDA's activity tends to be more focused on middle- and late-stage clinical trials although they also support product approval and post-marketing commitments. Global Antibiotic Research and Development Partnership (GARDP) works across all phases of drug development, with a focus on clinical development and post-market stages (National Academies of Sciences, Engineering, and Medicine, 2022). These funding mechanisms are invaluable for small and medium-sized AM drug developers with constrained operating capital. Experts interviewed for our 2018 study agreed that push incentives have been very successful in re-invigorating the AM drug pipeline.

An ancillary benefit of these push incentives, has been their ability to stimulate conversations in the investment community, leading to potential investors becoming interested again simply from the publicity about the funding and the ability for the company to argue that the funding represents government support and belief in their AM drug development program. The funding provided by organizations like the NIH, BARDA, and CARB-X can also provide external validation for the companies that are developing new AM drugs.

While these push incentives are beneficial, they are viewed as being insufficient to lure large biopharmaceutical companies back into the AM drug development space. According to developers and investors interviewed, push incentives fall short of addressing the more substantial concerns of large biopharmaceutical companies, such as a clear path toward commercialization, high revenues (or at least revenue growth over time), and a guaranteed return at market launch.

Pull Incentives

Transferrable Vouchers

A transferrable voucher for an extra year of marketing exclusivity could be effective in attracting larger pharmaceutical companies who would be able to use the voucher for a more profitable drug in their portfolio than the AM drug that won them the voucher. Venture capitalists we interviewed for our 2018 study expressed doubt that large pharmaceutical companies would plow revenue from a transferrable exclusivity voucher back into AM research and development. However, the availability of this voucher could create a positive investment atmosphere that would lead other biopharmaceutical companies and AM drug investors back into the market. As transferrable exclusivity vouchers would most likely be used by biopharmaceutical companies on blockbuster drugs, one expert interviewed expressed concern that the returns to the company would outweigh the benefits to society. For example, if the voucher were used on a blockbuster drug currently generating $20 billion per year in sales, it is unlikely that a novel AM drug would generate social returns equaling $20 billion and it would be viewed as unfair by competitors whose generic products were timed to launch when the blockbuster drug's (initial) marketing exclusivity period ended.

Subscription Model

Pull incentives that guarantee that a company can get an adequate return on investment have received increasing attention in recent years, especially as the UK's National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) are piloting a pull incentive - the subscription model. This is a type of market pull incentive that makes installment payments to the AM drug company for unlimited use of its drug for a specified duration and delinks the value of the drug from volume sold (Dall, 2022). The pilot project tests the concept of paying a subscription fee for two AM drugs, cefiderocol and ceftazidime-avibactam, and they are in the final stages of the pilot (P1, P2). NHS recently issued a draft guidance on how to estimate the full value of these two AM drugs, which will guide discussions on how much the NHS should pay AM drug companies under the subscription plan. The prices for the AM drugs are confidential but were set carefully to encourage use but not overuse (P1, P2). One drawback is the assessment of which AM drugs will be needed in the future and the focus on those drugs as opposed to other drugs in development. There is risk in that delay, as a different drug could be needed as AMR evolves in the future, or use of the drug could be higher than expected and companies would be expected to supply that quantity (P1, P2).

Sweden also initiated a partially volume-delinked subscription model. Sweden's model, however, is slightly different and establishes a contract for availability with manufacturers of recently approved drugs that have limited sales and address pathogens on the WHO's critical list (Rex, 2020). Sweden will pay a guaranteed revenue per year for a given quantity of the drug under that program. One early stage drug developer we interviewed for our 2018 study suggested a BARDA- and FDA-led pull incentive building on the success of BARDA in funding early stage and late stage developers. Another interviewee expressed concern that government pull incentives may be perceived as HHS or BARDA "picking winners" and would not be palatable politically.

A slightly different version of the subscription model was also suggested by the experts we interviewed in 2018 where users (e.g., healthcare facilities) pay a licensing fee for the use of the AM drug independent of volume used. Experts noted that the model could be designed to switch to usage-based payments if the use exceeds a pre-determined annual quota (e.g., due to an infectious disease outbreak at the licensee's healthcare facility). This would give large biopharmaceutical companies a lower bound on the return they could expect but would retain the potential for the drug to make multiples of that lower bound if there were an outbreak, epidemic, or another market

force that caused the drug to be prescribed more. Retaining such a "unicorn" upside (i.e., possibility of unusually high returns) was viewed as being important due to the number of investors in the biopharmaceutical space that invest because of the potential for hitting a huge return.

Market Entry Rewards (MERs)

Market entry rewards (MERs) structured as cash transfers to AM drug developers, which are conceptually similar to the subscription model described above, were viewed positively by the drug developers and early stage investors we interviewed in 2018. They agreed that the incentive, if the reward were sufficiently high (between $900 million and $2 billion), would draw large biopharmaceutical companies back into the AM space. One interviewee estimate for a sufficient MER was $2 billion, partly paid by other governments, which could lower the U.S. taxpayer burden. Another expert interviewed thought a reward of $300 million per year disbursed over three years ($900 million total) would be sufficient. One expert described MERs as "giving companies who are hemorrhaging money during development a lifeline and creating a clear path for the drug to succeed (in the market)," thus making large biopharmaceutical companies and venture capitalists more inclined to invest in this space. These experts did not, however, provide the basis for their estimates of the size of the award. Okhravi et al. (2018) conducted a simulation study to explore the effect of a MER on market approval of a new AM drug. Their results indicate that a fully-delinked MER between $600 million and $1.5 billion and a partially-delinked MER between $200 million to $1.25 billion improved an AM drug's likelihood of reaching market approval. Okhravi et al.'s study also indicated that projected revenues are a much stronger indication of an AM drug's likelihood of reaching the market than R&D costs (Okhravi, et al., 2018). The authors of the study also noted that the success of a MER program is tightly coupled to the characteristics of the target AM drug and other market conditions for that drug (Okhravi, et al., 2018).

In addition, venture capital firms and developers interviewed in 2018 also saw challenges with implementing these pull incentives and offered some alternatives that might be more effective than the transferrable voucher (discussed above), or MER as a long-term investment solution. Some concerns that were raised involving these pull incentives included the optics involved with implementing these policies from a public opinion perspective. An award given to a large biopharmaceutical company paid for by taxpayers or granting a patent extension to a company that does not use the profit from the award on more research and development for AM drugs, would not be perceived favorably by the public and so support for the policies may be hard to attain. In addition to the problem of optics, there is some doubt as to whether these policies would be enough to entice large biopharmaceutical companies to invest in AM development. A criticism of the MER and transferrable voucher is that these mechanisms are one-time rewards that do not establish increases to revenue streams on an ongoing basis, which may be key to convincing large biopharmaceutical companies of the value of investing in AM development today.

During our 2022 interviews, we asked experts to consider MER programs that delink payment for AM drugs from level of use as an intervention that can address the economic challenge of bringing AM drugs to market. We asked whether they preferred a given model, risks to consider, and how to ensure that only truly novel AM drugs with added clinical benefits are awarded payment.

As a first step, we have to recognize that there is a limited commercial market for most AM drugs and thus other ways have to be found to fund development (F1). We also heard this during our conversations with AM drug developers in 2018, as novel AM drugs rarely have revenues greater than $50 million per year, making it difficult to achieve profitability in a timeline that is acceptable to investors. Investors we interviewed indicated that they are drawn to projects with a higher probability of a short-term return, such as oncology and orphan disease drugs. Hence, in

order to bring large biopharmaceutical companies back into the market, a pathway and financial guarantees have to be provided (F1). A good model for this process might be the pneumococcal vaccine Advance Market Commitment (AMC) by Gavi, the Vaccine Alliance (A1). Gavi provides a legally binding forward commitment to manufacturers to purchase the pneumococcal vaccine according to predetermined terms funded through donations by several governments and the Gates Foundation. The manufacturers of the vaccine are provided a limited purchase guarantee, which removes some of the risk of investment for the manufacturer and incents them to invest. In exchange, manufacturers commit to supply the vaccine at a price affordable to developing countries, and Gavi subsidizes this price for approximately the first 20 percent of vaccine doses, enabling companies to recover their investment costs (Cernuschi, et al., 2011).

Some experts interviewed believe that the current failure of the AM drug market to develop a sufficient number of drugs will not resolve without market pull incentives or government interventions. Some think delinked market models are key to increasing the number of available AM drugs because innovators are guaranteed a profit (O1). The current business model incentivizes overuse, and an MER could counteract that incentive (A2). Furthermore, it could act as a mechanism to get a drug on the market for a small population of patients in which it has shown to be effective (A2). While some experts think that delinking the return from investment from the volume of prescriptions sold can be helpful, policy concerns will need to be addressed (A1, A2, A2, A2), the program needs to be easy to understand (BC1), and careful thought needs to be given to how the money is allocated (BC2). Several experts mentioned offering priority review vouchers, including for pediatric studies,, as the reward (BC1, BC3, F1). As noted previously, these vouchers can be used for any drug, come with rights to a faster FDA review and can be transferred and sold, making them very valuable. For example, BioMarin Pharmaceutical recently sold their priority review voucher for $110 million (Biomarin Pharmaceuticals, 2022). Some say the reward should be pegged to the utility of the drug (A2). If pegged to utility, it will also be profitable to make companion diagnostics for the drug (A2). CARB-X uses milestone awards, where the reward is provided along the way (A1). While CARB-X only operates in early-stage development, MER programs should also provide awards when milestones are achieved during the drug development process, as lump sum awards can limit incentive (A1). Given the riskiness of research and development of pharmaceuticals, companies will look for this in any MER program. Progress will also need to be evaluated by the payee along the way (A1). This might be addressed by providing payments along the development timeline based on when predefined milestones are achieved, as it balances the risk for the company and the payee. The risk with this type of reward structure, however, is that many products never make it to market, but funds would still be spent on those products. F1).

Others think that MER models will not work, given that there are more lucrative alternatives available in other markets (BC2). Experts discussed a number of challenges with these models, including the following:

- **Infeasibility of full de-linkage.** The MER model would not result in full de-linkage of sales from volume, because of the NTAP mechanism. NTAP is another pull incentive that is not delinked and will continue to be available (O4). It is also unclear how these models will affect pricing in the private sector (O4) and whether overuse would be prevented (A1).
- **Lack of accessibility for small companies.** MERs can be too onerous for small companies to access, depending on the manner they are structured (BC1).
- **Lack of transparency**. The requirements for receipt of the MER should be clear and consistent to keep companies interested (BC1).

- **Difficulty in establishing eligibility criteria and reward amount.** The level of innovation needed to obtain the reward is difficult to define (A1, A2, A2, A2, O3). This may result in an AM drug which is not urgently needed receiving a MER unqualified. One expert noted that, at a minimum, the AM drug must be novel and be effective in treating AMR in gram-negative bacteria (A1). Development can take 15 years or more and during this time, AMR and public health needs continue to evolve (Theuretzbacher, 2017). Theuretzbacher (2017) notes that a workable definition of innovation will be key for these types of policy initiatives to work. Regardless, it will be difficult to predict which AM drugs will be needed in the future and therefore selected for the program (O2). Bacterial infections need short-term treatment and are too unpredictable to determine which AM drug and how much of it is needed, as well as how much should be paid for it, making it difficult to implement the MER mechanism (A2).
- **Lack of sustainability**. A MER mechanism will not sustain AM drug development (A1, A2, A2, A2) as there is no incentive to continue innovation because another MER is needed to do so (O3). It is a short term, not a long term solution (O3).
- **Need for clinical evidence that shows innovation.** One expert noted that developers tend to prioritize speed over developing clinical evidence that shows innovation in developing AM drugs, resulting in AM drugs that are not any better than existing treatments (A2). Clinical evidence that shows that the AM drug is an improvement over existing treatments should be prioritized when establishing criteria for MERs. The government could make it a condition that the drug will be withdrawn if this clinical evidence cannot be provided in a timely manner by post-market approval studies (A2, A5) and will require quality review and control by FDA (A2, A5). Evidence should be provided that the drug is novel and provides an added clinical benefit (A2, A5). There is risk in that the reward will not generate the AM drugs needed because companies will just pursue the incentive without providing a product that is innovative or one that addresses an unmet need (BC2, BC3). That may require a new approach, such as using a CTN, which could be used to show superiority over other available AM drugs (O1). If AM drugs that are not novel are selected for a MER, this would be the wrong signal to the market and would result in a continuation of the current problems in AM development (O4).
- **Insufficient for post-approval requirement expenses.** The MER primarily funds the development of the drug and provides guaranteed market returns, but do not necessarily include the high cost of post-approval requirements (O3). Funding is needed beyond the MER to conduct safety surveillance, pharmacovigilance, and any other post-market regulatory requests (Daniel, et al., 2018). This could possibly be addressed by the criteria of the award.
- **Too costly.** In one expert's opinion, one type of MER model, the subscription model as designed by NICE in the UK (described earlier), is not likely applicable in the U.S., as it would be too costly for the government to pay the share that the U.S. would need to pay based on GDP (A1).
- **No guarantees for improved patient access.** These models do not increase patient access to the AM drugs (O2).

Reimbursement Changes for AM Drugs

CMS's New Technology Add-on Payment (NTAP) program provides additional payment for new drugs or medical devices that demonstrate significant improvements over existing technologies but have higher costs than the standard DRG (Diagnosis Related Group) amount. The

program is intended to offset the financial burden that hospitals may face when using these new technologies, and payments may be available for two to three years. Since its introduction in 2000 through 2020, only three AM drugs (fidaxomicin, meropenem-vaborbactam, and plazomicin) have qualified for additional payment under the program (Schneider, 2020).

According to the experts we spoke to in 2018, however, NTAP did not work because hospitals did not fully take advantage of it. For example, FDA approved Achaogen's AM drug, Zemdri (plazomicin), for the treatment of complicated urinary tract infections in June of 2018. According to Achaogen's press release, the NTAP program provides hospitals with a payment, in addition to the standard-of-care DRG reimbursement, of up to 50 percent of the cost of Zemdri for a period of two to three years. CMS assigned a maximum payment of $2,722.50 for a patient treated with Zemdri. Medicare add-on payments for NTAP technologies do help compensate hospitals for using new AM drugs such as Zemdri, but for the drug developers and venture capitalists we spoke with, the relatively modest add-on payments were insufficient to make the commercial prospects for AM drugs more promising.

In recent years, CMS made changes to the IPPS (Inpatient Prospective Payment System) to increase the number of AM drugs that may qualify for NTAP and to improve the reimbursement rates for hospitals that use these drugs. These changes included waiving the requirement for substantial clinical improvement for qualifying AM drugs, providing higher reimbursement rates for certain resistant infections, and increasing the reimbursement rate for hospitals using qualifying AM drugs under the NTAP program. More specifically, in addition to only having to show novelty and the AM drug exceeding the cost of the DRG, CMS raised the NTAP reimbursement to either the lesser value of 75 percent of the costs that exceed the DRG or the cost of the AM drug (Schneider, 2020).

During our 2022 interviews, one expert noted the successful use of the NTAP program by several hospitals (O2). This expert suggested investigating the success of these hospitals in using the NTAP program to see if it could be replicated elsewhere. It is likely that the practices and/or systems at these hospitals allow them to fully make use of the NTAP mechanism (Schneider, 2020). More could be learned about how to make the NTAP mechanism more beneficial for AM drugs by investigating the practices at hospitals that have benefited from NTAP. Others, however, remain skeptical of NTAP's ability to serve as a sufficient pull incentive because the period for payment is finite (Schneider, 2020).

Purchasing AM Drugs for the Strategic National Stockpile

The Administration for Strategic Preparedness and Response (ASPR) maintains a Strategic National Stockpile of medical products, including AM drugs. The stockpile is intended to provide protection in the case of a bioterrorism or nuclear attack, or against an infectious disease outbreak. We asked experts to assess the importance of having a stockpile to address increased demand in the event of a drug-resistant bacteria outbreak, and what features are important to include in such a program.

Having stockpiles of AM drugs allows the US government to quickly respond to increased demand for these drugs in an emergency. By tracking emerging threats and stockpiling drugs that are effective against them, the government can be prepared to address these threats when they arise (A1). One way to do this is through a prize system, which would incentivize companies to manufacture the needed drugs (A1). Alternatively, the government could buy out the company and hold the product itself (A2). While stockpiling can be costly for the government, it could serve as a pull incentive for AM drug companies (BC1, BC2, BC3). However, sales to the national stockpile may not be sufficiently large to keep an AM drug company financially afloat (O3).

The uncertainty associated with how AMR will evolve makes it difficult to predict what to stockpile (A1, O1, O4). Clinical studies that demonstrate the added benefits of drugs and better monitoring of drug-resistant infections are necessary to ensure that the stockpiled products can treat resistant infections (A2). Some experts interviewed suggested that instead of developing a stockpile, it would be more effective to track the evolution of AMR and focus development and manufacturing efforts on these trends (BC2, BC3).

4.4.3.3 Open Source Approach to AM Drug Development

Klug et al. (2021) noted that once we abandon the market as the prerequisite to drive AM drug development, other ways to conduct research can be explored. This includes an openly collaborative mechanism, as was effective for the research and development that was part of the response to the COVID-19 pandemic. We asked experts whether they consider an open source approach to AM drug development, in which all data and ideas are shared, and advances are not protected by intellectual property patents, to be a feasible option.

In general, most of the experts interviewed did not think that the open-source model would work for the AM drug market, as removing the intellectual property protection removes a key incentive (BC1, BC2, BC3). Large biopharmaceutical manufacturers and small biotech companies have different objectives. Work could potentially be shared before identification of the molecule, but once identified, intellectual property rights are very important (A4, A5, BC3, O1, O2), unless the industry became very consolidated (O3).

One expert noted that patent pools have had some success in HIV research (A3). The Medicines Patent Pool is a United Nations-backed public health organization which works by having patent holders voluntarily license their patents to the pool under certain conditions. The Pool then makes the license available to qualified generic drug manufacturers, which pay royalties on sales of the medicine in developing countries (World Intellectual Property Organization, 2011). Another expert suggested that it would be helpful to share failures, which are currently kept secret (A1).

4.4.4 Topics Related to AM Drug Development – Other Issues

4.4.4.1 Lessons from COVID-19

The market for AM drugs is smaller and vaccine development is different from AM drug development, but like COVID-19, AMR is a global threat, and the lessons learned during the pandemic may be useful for AM drug development. For example, the public-private partnerships that were formed to respond to the COVID-19 pandemic, such as the partnership between the U.S. government and Moderna, were successful in meeting the urgent need for vaccines and other treatments (O1, O3, A2) (McCarthy, 2021). Some experts believe that partnerships developed for other diseases, such as malaria and tuberculosis, are more relevant for AM drugs than the partnerships developed for COVID-19. For example, the TB Alliance uses a network of contract research organizations and large biopharmaceutical companies for the process chemistry and manufacture of TB drug development (A2) (TB Alliance, 2022a). The partnerships developed by the TB Alliance have been successful, as it has built the largest portfolio of TB treatments in history (TB Alliance, 2022b) (see also Section 4.4.4.2 below).

Experts noted that while AMR evolves much more slowly than a viral pandemic like COVID-19, the willingness of regulators to work closely with companies is helpful (O1, BC1, BC2). The transparency of the government and its emphasis on clinical evidence during COVID-19 vaccine development were also beneficial, as it is important to set clear and fair standards for products (A2). Policy makers were able to overcome regulatory hurdles and uncertainty during the COVID-19 pandemic, which could be useful for future responses (BC1).

The COVID-19 response effort was successful, but it required significant funding (F1). Federal funding helped accelerate the science, but going forward, the government should ensure that its funding comes with a stipulation that gives the government ownership of the science (A2),

Use of platform trials,[14] which compare multiple interventions against a single control group, increased during the COVID-19 pandemic (Vanderbeek, et al., 2022). Platform trials could also have value for AM drug development, but their transferability is limited because AMR is not widespread (A1). Some experts suggested the use of clinical trial networks (CTNs) similar to the European Clinical Research Alliance on Infectious Diseases (ECRAID) or other organizations, with adjustments to conduct small-scale trials that can demonstrate the superiority of new AM drugs (O1, O5). Others do not believe that CTNs would be useful because the surge in cases seen with COVID-19 is not something that is seen with drug-resistant infections (O3). Rapid deployment clinical trials, which are clinical trials that can be set up quickly in response to infectious disease outbreaks, might be a better option, but there are challenges with this approach that need to be addressed (O3).

Another major lesson that we can learn from COVID-19 is that societal behavior often only seems to change when a situation becomes dire. Recognition of the urgency of a problem is important but better communication of the problem to the public is also needed (BC1, BC2). Similarly, infection control and capacity for surveillance are of high importance, as was experienced during the COVID-19 pandemic (BC2). Infection control also needs attention in low- and middle-income countries so that resistant bacteria do not have a chance to develop (O1).

4.4.4.2 Public-private Partnerships (PPPs) and Non-profit Organizations (NPOs)

Public-private partnerships (PPPs) might be beneficial in developing nontraditional products, although it is likely that revenue generation will be problematic for these as well if the patient populations for these products are small (Cama, et al., 2021). We asked experts their thoughts about the success likelihood of PPPs and non-profit organizations (NPOs) in supporting the development of novel AM drugs.

Most experts believe that a partnership between the private and public sectors would be beneficial for the development of AM drugs (A1, BC1, BC3). NPOs alone are not capable of driving this development (A1, BC1, BC3). The biggest challenges are the complexity and expense of AM drug discovery, and the lack of market incentives, which cannot be addressed by NPOs alone (A1, BC1, BC3). Both a public commitment and private sector support, including access to capital, are necessary (O1, O2). The private sector has valuable expertise in drug development, while the government could support other aspects, such as stewardship, manufacturing, safety reporting, and pediatric studies (A1, O1, O2, O3).

PPPs, on the other hand, can be helpful (A4). Examples include the success stories of Moderna, which partnered with the US government during the COVID-19 pandemic and the PPPs for tropical diseases in low-income countries (A5). Another example is that of the TB Alliance, which partnered with generics manufacturers to produce the new BPal (bedaquiline, pretomanid, and linezolid) regimen of drugs for treatment of multi-drug resistant tuberculosis (MDRTB) (F1) (TB Alliance, 2022c). The TB Alliance, with support from the Bill and Melinda Gates Foundation, led pretomanid, as part of the BPaL regimen that included two marketed drugs (bedaquiline and

[14] A platform trial, also known as a basket trial or umbrella trial, is a clinical trial design in which multiple interventions are tested against a single control group simultaneously, speeding up identification of effective treatments. Platform trials are often used for diseases that have multiple subtypes or when there is a need to compare multiple interventions against a common control. For example, a platform trial could be used to evaluate the effectiveness of different drugs for treating different subtypes of cancer. Traditional clinical trials test a single intervention against a control group (Park, et al., 2019).

linezolid), through FDA approval. The TB Alliance collaborated with a network of partners, both public and private, to initially test different combinations in nonclinical platforms. Then, the Bill and Melinda Gates Foundation funded the clinical work. Commercialization was achieved through partnerships with various generic manufacturers, including Mylan, Macleods, and Hongqi Pharmaceuticals (TB Alliance, 2020). Further, to make the BPaL product available globally, the TB Alliance was able to lower costs by 85 percent (F1). For reimbursement, the product had to be reviewed by the WHO Global Fund and then could be procured by countries by means of tenders (F1). This approach to drug development could also be applied to the development of novel AM drugs for treatment of drug-resistant infections (F1).

Product development partnerships play a role in improving AM drug development but are only a component, as they do not change the innovation ecosystem (O4). One challenge is that the participation of large biopharmaceutical companies is needed for the tail-end of development and commercialization (A5). One type of partnership that may prove useful, as it has for TB drugs, are manufacturing facilities which partner with non-profit drug developers (O4). Another example of these types of partnerships is Civica, which is a non-profit organization that procures and manufactures the generic drugs needed by its hospital members (O4). This is a public endeavor supported by private entities, and the first two drugs it produced were AM drugs (O4). This kind of partnership allows organizations to control their own supply. These partnerships could support companion diagnostics and clinical trial platforms that have already been built (although some of these would need to be retrofitted for AM trials) (O4).

4.4.4.3 Manufacturing Capacity for AM Drugs

During the COVID-19 pandemic, there were reports of shortages of certain medications and medical supplies, which may have been due to a lack of manufacturing capacity. In addition, the AM drug market also experiences supply chain disruptions from time to time, resulting in spot shortages, which drive up prices (A2, O4). Compared to other drugs marketed in the U.S., AM drugs are 42 percent more likely to experience shortages (USP, 2022). For example, cephalosporins, which are on WHO's list of critically important AM drugs, are at elevated risk of shortage, with 40 percent of the active pharmaceutical ingredients currently in shortage due to pricing issues (USP, 2022). According to FDA's drug shortage database, several AM drugs are currently (as of December 2022) in shortage, including amoxicillin oral powder for suspension, metronidazole injections, rifampin injections and capsules, and rifapentine tablets (FDA, 2022). Therefore, we asked experts if it is necessary to address manufacturing capacity for AM drugs now in order to be prepared for potential surge needs during a public health emergency.

Most interviewees agreed that it is important to have a plan for manufacturing capacity for AM drugs in case of a surge need (A1, A3, A5, BC1, BC2, BC3, O1, 02, 03, 04). Currently, most of the AM drug manufacturing capacity is outside the U.S. For example, China provides approximately 90 percent of the global supply of inputs needed to make generic antibiotics that treat bronchitis, pneumonia, pediatric ear infections, and life-threatening conditions such as sepsis (Gibson, 2021). Most AM active pharmaceutical ingredient manufacturers are in India and China; combined, the facilities in these countries manufacture 58 percent of AM active pharmaceutical ingredients (USP, 2022). Government could subsidize U.S. manufacturing to provide surge capacity as well as health security (BC1, BC3, O3). An example of a program like this is BARDA's Project BioShield, which is providing funding for Paratek's construction of a U.S. supply chain for the manufacturing of omadacycline, among other provisions (Blankenship, 2020). One expert noted that this capacity could be shared with other small molecule manufacturing plants (BC3). The goal should be to move from batch to continuous manufacturing, but this is difficult and expensive (A1). The manufacturing capacity could also be on-demand manufacturing using real-time data and 3D

printing techniques (O3).[15] Diversity of the supply chain is also important in case a region is affected by a disaster (O1). Manufacturing capacity should be able to accommodate increased demand during times of surge, but also be flexible enough to be repurposed for other needs when demand is not as high. (O4).

One proposal is to maintain knowledge and manufacturing capacity for certain AM drugs in case resistance arises. However, certain AM drugs require specialized facilities, such as non-penicillin beta-lactam-based products, which require separate production facilities (U.S. Food and Drug Administration, 2013), and the offshore location of many facilities may make this difficult (O3). At least one expert suggested that more public investment is needed to support manufacturing of older drugs and to stabilize supply chains to address this issue (A2).

4.4.5 Summary

Table 3 summarizes the market challenges and possible interventions that experts discussed during our interviews. As noted in the table, some groundwork has already been done for several of these, which could be further examined to assess the potential benefit of the interventions. Many of the interventions listed are more conceptual and need to be developed in greater detail (e.g., forming a new government entity and strengthening surveillance systems). Several proposed interventions are also synergistic and therefore need sequential implementation, whereas others could be implemented simultaneously. For example, diagnostics will be needed for pathogen detection to effectively run CTNs and to establish evidence of superiority, which would help physicians to encourage use of a new AM drug. This may also require the development of new diagnostics if existing diagnostics cannot be used.

Table 3. Possible Interventions to Address AM Market Challenges as Suggested by Experts Interviewed in 2022

Market Challenge	Intervention	Existing Data to Support Intervention
Market structure, conduct, and performance of the U.S. AM drug industry	Remove AM drugs from the DRG reimbursement system	Some success with the NTAP system
	Change to a market model delinked from sales	UK/Sweden testing these market models
	Subsidies (e.g., in form of priority vouchers)	Already in use to encourage development of drugs for neglected diseases
	Formation of new public entity to manage AM drug portfolio	
Insufficient clinical evidence on added clinical benefit at time of regulatory approval	Use of diagnostics and clinical trial networks	HIV Clinical Trial Networks, National Cancer Institute National Clinical Trials Network
	Test for superiority rather than non-inferiority	
	Focus on patient outcomes rather than pathogens	

[15] In pharmaceutical manufacturing, 3D printing using real time data refers using 3D printing technology to produce pharmaceutical products using data that are collected and processed in real time. This enables customized production of personalized medication, as well as faster and more efficient on demand production. This can be particularly useful for the production of rare and orphan drugs, allowing production of small batches of specialized medications. Additionally, 3D printing can reduce the cost and complexity of drug manufacturing and can make the production of medications more flexible and adaptable (Ong, et al., 2022).

Market Challenge	Intervention	Existing Data to Support Intervention
	Develop new platforms for discovering new drugs	
	Provide information to physicians about AM drugs	
Small market size – relatively low number of drug-resistant infections in the U.S.	Categorize some AM drugs as not profitable and use a not-for-profit business model for development	
	Assist small drug companies with access to larger foreign markets.	
Threat of an increase in antimicrobial resistance (AMR)	Development of diagnostics	Employed by other countries to manage AMR (e.g., Norway and Sweden)
	Greater oversight of stewardship programs	
	Strengthening surveillance systems	
	Increased investments in policies that combat AMR (e.g., limiting use of AM drugs in agriculture, improvements in hygiene)	
	Development of anti-virulent drugs	

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APPENDIX A: INTERVIEW GUIDE

The lack of available AM drugs to meet current and future threats of AM resistance is often attributed to a number of inefficiencies in the AM drugs market. According to Spellberg (2014), the causes of these inefficiencies can be divided into scientific, economic, and regulatory barriers and there may be others. The barriers include:

- Scientific barriers such as a lack of innovation that leads to drugs in the pipeline that are modifications of already existing drugs (which will not be able to address the problem of AM resistance in the long term),
- Economic barriers such as high research and development costs and low prices, DRG reimbursement, short treatment duration, and AM stewardship,
- Regulatory barriers such as burdensome clinical trial design.

These are common discussion points to explain the difficulties in bringing AM drugs to market.

ERG has been contracted by the US Department of Health and Human Services (HHS) Office of the Assistant Secretary for Planning and Evaluation (ASPE) to evaluate the inefficiencies in antimicrobial drug markets. The objective of our research is to identify AM drug market inefficiencies that may be candidates for government interventions to correct those inefficiencies. To this end, we have developed a list of questions to probe issues beyond those most commonly discussed where government intervention may play a role, as follows:

1. Beyond the issues most commonly discussed (lack of innovation, low returns, etc.), what are the challenges facing the U.S. AM drug market? What type of government interventions can be instituted to alleviate these challenges?
2. Large biopharmaceutical companies have withdrawn from direct investment in AM drug development but are still investing indirectly (e.g., AMR fund). What do you think their continued interest is driven by?
3. The preclinical pipeline for AM drugs is diverse, with many promising scientific concepts. Based on the 2020 WHO report on the global preclinical AM pipeline, currently there are 292 preclinical candidates across many new modalities (vaccines, antimicrobial peptides, bacteriophages, virulence inhibitors, immunomodulatory compounds) plus evolution of existing mechanisms. In addition, nanotechnology is being studied as a potential solution, including particles of liquid metal to shred bacteria and gold nanoclusters to inhibit bacteria.
    a. Do you think that innovation in the preclinical pipeline as just described can address the problem of AMR?
    b. Do you know of other promising innovations that could potentially address AMR?
    c. What can be done by government to encourage promising scientific discoveries in the preclinical pipeline to progress towards IND-ready candidates? Could changes in clinical trial requirements accelerate development and approval?
    d. How can early stage innovation in new technologies be encouraged?
4. Given the reported challenges in bringing AM drugs to market, should the government focus on developing a stockpile of novel AM drugs and/or AM drug technologies that can address AMR if there is a surge need due to an AMR public health emergency? If so, what features do you think are important in a program like that?

5. Do you think a Market Entry Reward (MER) program that delinks payment for AM drugs from level of use can address the economic challenge of bringing AM drugs to market (e.g., subscription model, prizes, etc.)?
    a. Do you have a preference for one of these models or another not named above?
    b. What are the risks associated with that model?
    c. How does one ensure that only truly novel AM drugs with added clinical benefit are awarded payments when robust clinical evidence for the drug's ability to meet an unmet need and/or treat life-threatening bacterial infections is lacking at the time of regulatory approval?
6. Product development partnerships that formed in response to COVID were helpful to meet surge need for the vaccines and other treatments. Are these type of partnerships transferable to AM drug development?
    a. If so, what lessons could be transferred to the development of new and novel AM drugs?
    b. What other aspects of what we learned during COVID might be useful to stimulate AM drug development to combat AMR?
7. Some have proposed the formation of public benefit corporations (a hybrid of for- and non-profit corporation). Others support the use of a fully non-profit model (e.g., GARDP is one example of such model that aims to develop five new AM drugs by 2025). What are your thoughts on the relative success of these types of models?
8. Some advocate adopting an open approach to AM drug research and development in which all data and ideas are shared, and advances are not protected by patents (Klug, et al., 2021). In your opinion, is such an approach economically feasible and palatable to an industry where intellectual property (IP) outcomes are the main metrics of success?
9. We learned from COVID that the government was not well-prepared to provide surge capacity in terms of available manufacturing facilities, although they subsidized manufacturing expansion for commercial firms. Do you think that manufacturing capacity for AM drugs should be addressed now to support manufacturing during a public health emergency and if so, how (e.g., expand domestic manufacturing capacity, building domestic supply chains, invest in advanced manufacturing techniques, etc.)?