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Models for Financing Antibiotic Development to Address Antimicrobial Resistance



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About Financial Innovations Labs®

Financial Innovations Labs bring together researchers, policymakers, and business, financial, and professional practitioners to create market-based solutions to business and public policy challenges. Using real and simulated case studies, participants consider and design alternative capital structures and then apply appropriate financial technologies to them.

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With an independent voice, FasterCures is working to build a system that is effective, efficient, and driven by a clear vision: working with our partners to build a patient-centric system where science is accelerated, unnecessary barriers are overcome, and lifesaving and life-enhancing treatments get to those who need them as rapidly as possible.

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INTRODUCTION

Often deemed a “silent pandemic,” antimicrobial resistance (AMR) is a growing threat to global health. AMR occurs when microorganisms (e.g., bacteria, viruses, fungi, and parasites) adapt over time and no longer respond to the medicines designed to treat infections. The importance of antibiotics is unquestionable. Deaths from infectious diseases are a fraction of what they were in 1928, when penicillin was first discovered.¹ But as existing antibiotics lose effectiveness against common infections such as strep throat, urinary tract infections, and methicillin-resistant *Staphylococcus aureus* (MRSA), the risks involved in necessary lifesaving procedures like surgery and chemotherapy increase.² If left unaddressed, AMR is expected to lead to increased rates of serious illness, preventable deaths, and prolonged hospital stays, not to mention higher health-care costs.³ The development and successful commercialization of novel antibiotics are thus vital to maintaining the very foundation of a healthy and operational society.

AMR’s threat to the integrity of our health-care system is alarming. A recent study by *The Lancet* estimated that drug-resistant infections were directly responsible for 1.27 million deaths

worldwide in 2019 and played a role in nearly 5 million deaths overall.⁴ A study commissioned by Britain’s prime minister estimated drug-resistant strains of malaria, HIV, tuberculosis, and other bacterial infections could eventually multiply that number to 10 million people annually, at a global cost of \$100 trillion.⁵ Antibiotic resistance, which refers more specifically to the threat posed when bacteria become resistant to medicines, is particularly concerning. According to the US Centers for Disease Control and Prevention (CDC), antibiotic-resistant diseases afflict more than 2.8 million people in the US every year and cause more than 35,000 deaths.⁶ The costs of these maladies are not limited to disease and mortality rates, either. The CDC estimates that first-line antibiotic treatment failures cost the US health-care system \$20 billion each year in direct costs and \$35 billion in lost productivity.⁷ If AMR’s current trajectory continues, the World Bank predicts that global GDP will decline between 1.1 percent and 3.8 percent by 2050.⁸

Although AMR is a natural process, it is accelerated by the inappropriate use of existing antibiotics. The overuse of antibiotics has been a considerable contributor to AMR. A study of 76

countries led by the (US) National Academy of Sciences found that the antibiotic consumption rate increased 39 percent from 2000 to 2015, and the number of defined daily doses jumped by 65 percent.⁹ New antibiotics are especially crucial to overcoming resistance. But numerous financial and regulatory barriers in antibiotic development and commercialization have caused most large pharmaceutical companies to exit the industry. Instead, they are focusing their efforts on therapeutic areas like oncology or rare diseases, where profits are linked to large sales volumes and/or higher prices and are thus perceived to be more sustainable and predictable. Antibiotic innovation is as capital-intensive as any other drug category, but it does not generate the kinds of returns needed to offset such large upfront investments because of the stewardship required to reduce resistance. Antibiotic development can cost as much as \$1.5 billion, but the median US sales of the most recently approved antibiotics were just \$16.2 million.¹⁰ As a result, many large pharmaceutical companies are no longer developing antibiotics, leaving biotech companies to fill the gap. More than 95 percent of the antibiotics in development are being investigated by small companies, two-thirds of which are doing so for the first time.¹¹ As smaller—and often single-product—companies, their path to profitability is long and paved with challenges.

Without the necessary incentives and financing instruments to encourage private investment in antibiotic innovation, the future of global health is ominous. In September 2021, the Milken Institute organized a Financial Innovations Lab

in collaboration with Wellcome Trust to explore innovative financing models to foster investment in novel antibiotics. The Lab brought together public and private investors, financing experts, pharmaceutical companies, and small and medium-sized enterprises (SMEs) in the biotech field to develop recommendations to expand the range and availability of investment opportunities and innovate new financing structures. Over the course of months of research, stakeholder interviews, and group convenings, Lab participants identified two key financing mechanisms that could drive new forms of capital to the space:

- Establishing a blended capital fund to attract and capture a wider pool of potential investors by offering different types of financing to adjust to the changing capital needs of an antibiotic as it moves through the stages of development.
- Pooling drugs into a bond structure similar to that used for traditional infrastructure investments. Participants designed an “antibiotic bond,” in which committed subscription payments would provide the capital to pay back investors.

To move either idea forward, participants agreed there must be a federal government guarantee to address antibiotic development. Therefore, the models assume and integrate financing provided from the proposed PASTEUR Act in the US (see below) and other revenue-guaranteeing programs globally. The following report discusses the state of the antibiotic market and development pipeline today and proposes a structure for these two financing models.

ISSUES AND PERSPECTIVES

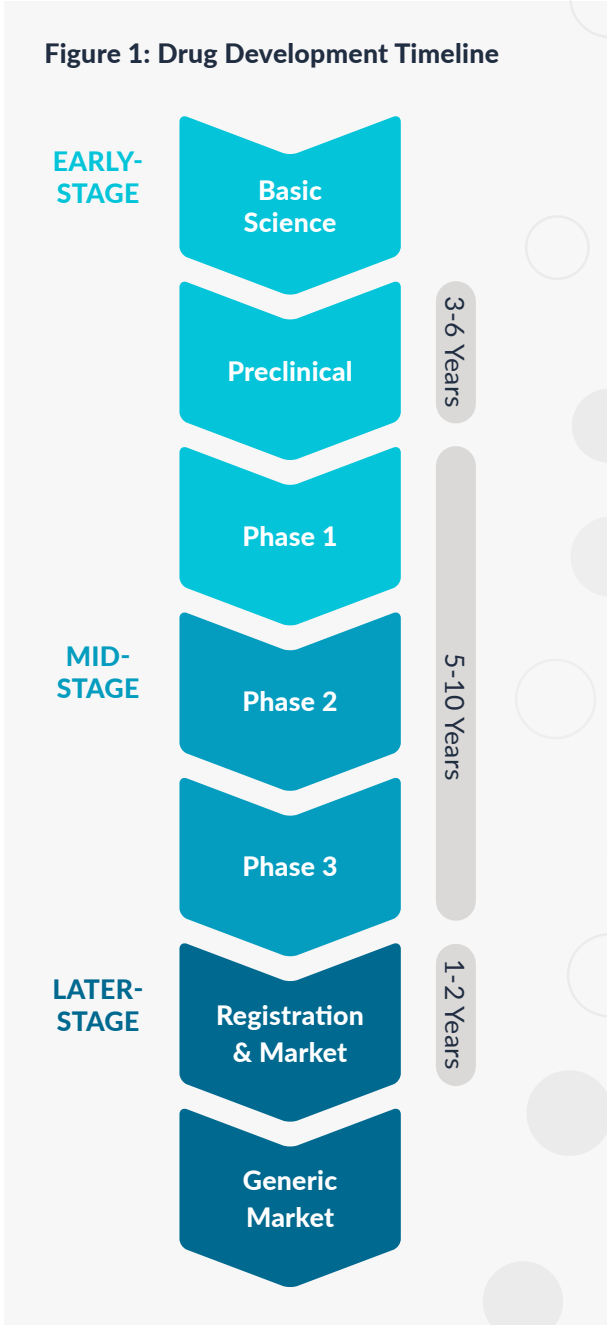
The focus of this work is to address the economic challenges of bringing new antibiotics to market. While a host of programs are instrumental in keeping the R&D pipeline afloat, today’s market function poses significant obstacles for companies trying to finance the continued development of novel antibiotics. To overcome these barriers, all stakeholders must appreciate the importance of having effective antibiotics available for use and understand how their actions affect the overall landscape. For clinical stakeholders, that means reducing resistance by ensuring antibiotics are prescribed appropriately. In a survey by Pew and the American Medical Association, for example, 65 percent of doctors noted an increase in resistant infections but did not see themselves as directly involved in the problem.¹² On the financing side, it is estimated that the public sector will need to inject \$1.2 billion into the market every year to incentivize antibiotic innovation.¹³ That is a considerable cost burden for public resources, underscoring the need to address existing market failures and lower the barriers for private investors to play a role.

BARRIERS

General Barriers

Drug development timelines can be long, with unexpected barriers to investment popping up throughout the entire lifecycle of antibiotic development. It takes upwards of a decade to bring a new antibiotic to market, and the cost to do so can exceed \$1 billion.¹⁴ The high risk of loss in the initial phases, in particular (defined in this report as preclinical and Phase 1), discourages investors from putting their capital to work.

The odds improve in the later stages of drug development (Phase 2, Phase 3, and registration & market periods), but these stages are very capital intensive. Even though there are streamlined pathways for antibiotics to gain approval, once they successfully reach the market, they face significant late-stage manufacturing costs and expensive



Source: Milken Institute (2022)

testing and post-market processes. Some of the required expenditures include pediatric studies, additional safety and pharmacokinetic studies (to understand how the body absorbs and metabolizes the drug), and ongoing pharmacovigilance (to identify and assess adverse effects). Additional expenses are not mandatory but are strongly

recommended because they increase the chances of commercial success. These include, but are not limited to, commercial antimicrobial susceptibility tests (which help detect resistance) and medical affairs activities such as sponsored research and speaker presentations to educate the field.¹⁵

The typical drug development model offsets early expenses with substantial commercial revenues from high-volume sales when the product reaches the market. Antibiotic development cannot follow those patterns. It can take 20 years or more for a new antibiotic to become profitable, and even then, the potential for achieving profits is severely limited because the more an antibiotic is used, the less effective it becomes as bacterial resistance increases.¹⁶ Antibiotics need to be used sparingly to reduce the likelihood of resistance and only prescribed for those patients who truly need them. Stewardship, the practice of holding novel antibiotics in reserve for use only in cases of last resort, further inhibits profitability because drug developers cannot count on a consistent market for earning a financial return on their investment.¹⁷ For antibiotics to be sustainable and profitable, the financial reward for innovators needs to move away from sales volume alone.

Misaligned financial incentive structures, especially in the US health-care system, contribute to the inappropriate use of antibiotics. Medicare reimburses inpatient hospitals a fixed amount for the bundle of services that are required to treat an individual with a particular disease. These services are categorized into Diagnosis-Related Groups (DRGs). Payments to hospitals are based on the average cost to deliver care to individuals within that DRG. If a hospital can effectively treat a patient for less than the fixed reimbursement DRG amount, it gets to keep the difference. To keep treatment costs as low as possible, hospitals often prescribe the cheapest antibiotics available, typically those that have gone generic, even when newer and more effective options may be available.¹⁸

The experience of Melinta Therapeutics is illustrative. Founded in 2000, the New Haven-based company brought four different antibiotics to

market after successfully moving them through the drug development pipeline. Each of Melinta's four antibiotics required roughly \$25 million in revenue per year to maintain a supply chain. Unfortunately, none of the drugs produced enough revenue to cover the supply chain expenses—not to mention the sunk costs of developing the drugs—and three of the four generated annual revenues of less than \$12 million apiece.¹⁹ At the end of 2019, Melinta was forced to declare bankruptcy because revenues could not cover operating expenses.

Financing Barriers

Typically, early-stage drug discovery is funded by public and philanthropic organizations, and conducted primarily by government or academic laboratories because the risk of failure is so high. Small- and medium-sized enterprise (SME) biotech companies like Melinta (often funded by venture capital and angel investments) then develop the discoveries that emerge from these laboratories in hopes of bringing a drug to market. Before antimicrobial resistance became a global concern, many big pharma companies had active antibiotic development programs. But because novel antibiotics need to be used sparingly in cases of last resort, the lack of a consistent market to provide a financial return on investment led many pharma companies to abandon their antibiotic programs.²⁰ As of 2021, only nine large research-based companies still had antibiotic development programs: GSK, Johnson & Johnson, Merck, Otsuka, Pfizer, Roche, Sanofi, and Shionogi.²¹ As buyout prospects for startup companies continue to dim, cautionary tales like that of Melinta will continue to signal to the traditional market that investments in antibiotic development are unlikely to pay off.

This has left development in the hands of biotech firms that do not have the balance sheet or development capabilities of a large multinational organization. Even if one of these firms has pockets deep enough to shepherd a drug all the way through the R&D pipeline, the large deficits they incur through the process, combined with the lack of visible commercial revenues, severely reduce the company's valuation. Research by Novo Holdings

found that the average share price for an anti-infective drug company fell 71 percent from 2018 to 2020.”²²

Some private SMEs take on any type of funding and financing possible, from expensive private equity to restrictive venture debt. While equity is common in traditional biotech investing, the expected rate of return on antibiotics does not usually impress investors. While not exclusive to SMEs in the antibiotic space, venture debt as a financing option has grown in popularity in recent years. Venture debt is cheaper and less dilutive than equity, and it tends to be patient capital, which aligns better with the long R&D timelines involved in antibiotic development. Even though revenue generation may be a few years off, SMEs in the later stages of clinical trials have more robust data packages that can provide lenders a level of confidence in writing the loans. However, the terms and conditions of venture debt are often not made public, discouraging subsequent investors from participating. If an SME’s balance sheet is too complicated, private investors will often pass on the opportunity to participate in the deal. And because venture debt is a loan, the providers have payback priority over most other forms of capital.

Investors are attracted to opportunities when they can quantify the expected financial or societal return on their investment. In the case of antibiotics, a novel drug benefits more than just an individual with the bacterial infection. Antibiotics reduce the spread of infections and limit the public health costs associated with an outbreak. Under the current market structure, companies developing antibiotics will need to attract new classes of investors. However, quantifying the public benefit to justify the cost of development is challenging. So far, impacts have been quantified to the downside: What is the negative result if the market lets the antibiotic pipeline dry up? Antibiotic developers must develop ways to articulate better the social and economic upside of a robust antibiotic pipeline. Researchers in Japan, for example, have modeled the clinical and economic outcomes of the country’s National AMR Action Plan. The study estimated the potential economic and lifesaving potential of reducing drug-resistant pathogens.²³

CURRENT ANTIBIOTIC FUNDING OPTIONS

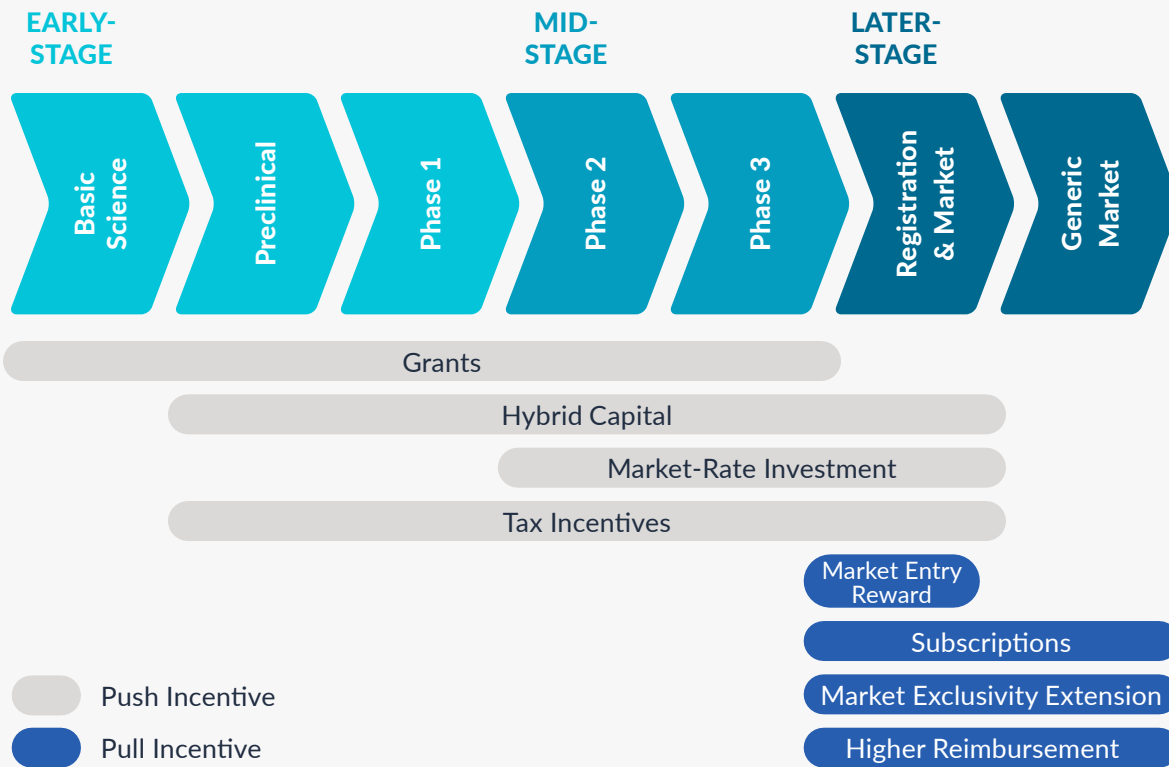
As any kind of drug progresses through development, the type of money required to sustain its development changes. As scientific risk is reduced, the scale of capital needed increases, and the probability of success of the drug becomes clearer and attracts new types of investors. But unlike the traditional biotech market, the antibiotic market requires financial incentives to encourage investment at every stage of development. These incentives are often categorized as push or pull incentives. Push incentives focus on paying for antibiotic research and development, while pull incentives focus on providing future revenue for approved products. It is widely recognized that a balance of push and pull incentives is needed to stimulate novel antibiotic development.²⁴ However, most of the incentives available today focus on the push side.

Push versus Pull Incentives

Today’s antibiotic funding market consists of both push and pull incentives. A push incentive encourages R&D by subsidizing or lowering costs, thus reducing the barriers to entry for small- and medium-sized companies that may lack the capital to “push” a drug all the way through development. Push incentives are usually provided by public or philanthropic resources that are more concerned with societal benefits than with maximizing profit. The monetary amounts needed for push incentives are generally well understood.

Once a drug reaches the later stage of the development pipeline, pull incentives are needed to create a market that rewards antibiotic developers for innovation without having to sell a large volume of the drug. Pull incentives broaden the pool of investors seeking to participate in the market by making opportunities more profitable than they would otherwise be in the free market. These incentives “pull” investors into the market.

Figure 2: Antibiotic Funding Options by Stage



Source: Milken Institute (2022)

Early-Stage Options

The vast majority of early-stage antibiotic development is funded through public or philanthropic money, primarily with grants that are not expected to be repaid. The Organisation for Economic Co-operation and Development (OECD) estimates that grant funding for antibiotic R&D totals \$550 million every year worldwide.²⁵ In addition to lowering barriers to entry for SMEs, grant funding can be extremely targeted to areas of greatest need.

One of the major government funders of early-stage antibiotic development in the US is the Biomedical Advanced Research and Development Authority (BARDA). The agency funds the development of medical countermeasures not only for infectious diseases but also for influenza pandemics and for chemical, biological, radiological, and nuclear accidents and attacks.²⁶ BARDA's Antibacterial Accelerator program provides non-

dilutive funding to offset developers' high R&D costs and offers technical assistance to reduce risk.²⁷ Although it does not fund basic science, BARDA supports companies developing antibiotics from the preclinical stage to marketing approval.²⁸ Since its launch in 2011, the program has provided \$1.5 billion in funding.²⁹ As of June 2021, BARDA's portfolio includes 16 antibacterial programs to address drug-resistant bacteria that the CDC and the World Health Organization (WHO) consider serious global threats.³⁰

As part of its strategy to advance new antibiotic development and reduce antimicrobial resistance, BARDA joined forces with the National Institute of Allergy and Infectious Diseases and funding partner Wellcome Trust in 2016 to co-found the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator, a global nonprofit public-private partnership known as CARB-X. In response to

appeals by the US and UK governments, CARB-X also receives support from the German government and The Bill & Melinda Gates Foundation.³¹ The platform provides non-dilutive grants, scientific expertise, and business support to companies developing innovative antibacterial therapies.³² CARB-X funds up to 90 percent of the costs involved in preclinical development and up to 80 percent during Phase 1.³³ CARB-X has allocated \$480 million between 2016 and 2022; projects must meet contractual milestones to progress to subsequent funding stages.³⁴

Government-supported programs have been essential in sustaining early-market development over recent years, but private stakeholders have also played a key role. In 2018, the Novo Nordisk Foundation launched the REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund to invest in companies involved in discovering and developing therapies to combat drug-resistant bacteria.³⁵ The fund has a total budget of \$165 million, with \$20 million to \$40 million allocated annually over a three- to five-year period.³⁶ Around 20 projects will receive funding of up to 100 percent of costs. The expectation is at least one new therapy will eventually reach the market.³⁷

The REPAIR Impact Fund is an example of another kind of push incentive known as a hybrid investment. Hybrid capital typically prioritizes social impact and flexible terms in exchange for financial gain or repayment. Most of the REPAIR Fund's investments come in the form of convertible loans, but the project also offers a non-dilutive royalty-based model for larger firms where the early-stage program is only a small part of the company's overall value.³⁸ The fund is designed to boost the initial development of new and innovative therapies rather than creating a large return to the firm. This seed money removes risk so subsequent investors can take the company through the later stages of clinical development to commercialization.³⁹

These early-stage options, among many others, are critical to moving antibiotics into clinical development. Incentives for the early stages of

R&D will remain necessary to push antibiotic products through development.

Late-Stage Options

Capital invested in the earliest stages of development is unlikely to be recovered since there is little to no visibility into the revenue potential of the product and because such a small fraction of antibiotics make it to the market. In the later stages, however, investors begin to understand the potential business case for a therapy. The goal of many players in the late stages of development is to reduce risk for investors willing to participate as the chances of an antibiotic's success become clearer. To improve the recyclability of capital, investors in these stages of development may structure push incentives as hybrid capital. Like grants, hybrid capital often supports R&D requirements. Push incentives structured as hybrid capital can take many forms:

- Venture philanthropy, a form of investment where the social return is the key priority, and any financial gains are reinvested into the business.
- Recoverable grants, which offer the funder the potential to recover capital if the recipient does not meet predefined goals. Some recoverable grants are structured so that capital is provided in milestone payments as progress is made.
- Below-market-rate investments, in which investors accept a concessionary financial return that may not be significant.

In July 2020, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) brought together more than 20 of the globe's leading pharmaceutical companies to create the AMR Action Fund, with the goal of bringing two to four new antibiotics to market.⁴⁰ With support from the Wellcome Trust, the European Investment Bank (EIB), and the World Health Organization (WHO), the fund intends to invest approximately \$1 billion into clinical-stage biotech companies and provide industry expertise to support novel antibiotic development.⁴¹ Funding will come in the form of equity or convertible debt.⁴² A vital

aspect of the AMR Action Fund is to buy time to allow governments to enact pull incentives or development models that will support antibiotic development over the long term.⁴³ The fund will start making investments and building its portfolio in 2022.⁴⁴

The goal of many players in the late stages of development is to reduce risk for investors willing to participate later. The InnovFin Infectious Diseases Finance Facility (IDFF) is another example of a late-stage hybrid fund. Introduced in 2014 by the European Commission and the EIB, it provides funding to developers of vaccines, medicines (including antimicrobials), medical and diagnostic devices, and novel research against infectious diseases.⁴⁵ The program uses several hybrid funding mechanisms, including standard debt such as loans, guarantees, and equity-type financing for amounts between €7.5 million and €75 million (around US\$8.7 million and \$87 million).⁴⁶ Loans reduce risk for drug developers because they are only paid back in the event of a successful project.⁴⁷ The IDFF covers the costs of Phases 1-3, commercialization setups like market access, prototype development and the rollout of novel equipment, preclinical R&D, and working capital requirements.⁴⁸ The EIB will continue to provide funding for projects countering infectious diseases until the end of 2022.⁴⁹

Hybrid investment options are not limited to the US and Europe. In 2015, Japan created an Agency for Medical Research and Development (AMED) to consolidate and manage biomedical research and grant funding.⁵⁰ AMED's signature Cyclic Innovation for Clinical Empowerment (CiCLE) program seeks to boost innovation and R&D for infectious disease and cancer projects⁵¹ by funding projects between ¥100 million and ¥10 billion (US\$875,000 to \$87.5 million) during any phase of the pipeline.⁵² These payments are interest-free, payable within 15 years, and allow for "flexible repayment options" (i.e., they require repayment only if the project's goal is met). If the goal is not met, only 10 percent of the funding needs to be repaid. AMED or the patent holder can also receive remuneration if the goal is achieved by charging for research results based on product sales.⁵³

In addition to grants, loans, and hybrid investments, governments may also use tax policy to lower upfront expenses and reduce the risks associated with antibiotic R&D. Tax incentives can benefit both public and private investors and can be implemented across the R&D pipeline. They can lower investment costs by reducing or eliminating the tax owed on any capital invested in antibiotic development. Tax incentives already exist in other markets like renewable energy development, so they are familiar to governments and investors alike. Currently, there are no tax incentives focusing explicitly on antibiotic development, but drug developers may benefit from existing tax schemes that support R&D in the overall biotech field.⁵⁴

For example, Recce Pharmaceuticals has received more than \$1 million in non-dilutive funding through a series of tax rebates from the Australian government.⁵⁵ The Advanced Finding awards have enabled Recce to recover 43.5 percent of its overseas antibiotic R&D costs between 2017 and 2022.⁵⁶ In the US, the Orphan Drug Act of 1983 allows the Food and Drug Administration (FDA) to award tax credits of up to 50 percent of R&D expenses to companies working on drugs that treat diseases affecting fewer than 200,000 people. In August 2021, Paratek Pharmaceuticals announced its antibiotic NUZYRA® (omadacycline) won orphan drug designation,⁵⁷ making it eligible to receive a tax credit of 25 percent for expenses of a qualified clinical trial.⁵⁸ Tax incentives are not limited to national governments, either. The state of Maryland, for example, offers the Biotechnology Investment Incentive Tax Credit (BIITC), a 33 percent income tax credit to individuals or entities that invest \$25,000 or more in a Maryland-based biotechnology company. The program offers additional incentives for investing in specific counties and opportunity zones across the state.⁵⁹

Industry partnerships can coordinate collaboration between public funding and private expertise. Organizations involved in antibiotic R&D may manage portfolios through investments in projects at universities, research institutions, or the private sector. In 2016, the WHO and the Drugs for Neglected Diseases initiative founded the nonprofit Global Antibiotic Research and Development

Partnership (GARDP) to develop novel antibiotics with a gap in their R&D.⁶⁰ An independent organization since 2019, GARDP is a global public-private partnership that works with 60 partners in 22 countries, including governments, the pharmaceutical and biotech industries, academia, civil society, and even individuals impacted by infectious diseases.⁶¹ When new antibiotics become available, GARDP works to ensure they are used responsibly and are affordable and available to those in need.⁶²

Funded by both public and philanthropic sources, GARDP leverages grants and incentives like milestone payments.⁶³ While GARDP funds across the antibiotic development pipeline, it focuses primarily on late-stage clinical development.⁶⁴ The program does not offer loans or equity.⁶⁵ Rather, it uses financial tools like in-licensing, intellectual property, acquisition, and co-funding to speed drug development.⁶⁶ As of the end of 2019, GARDP had secured €90 million (around US\$104 million);⁶⁷ it seeks to raise €500 million (US\$580 million) by 2025 to develop five new drugs that address the infections posing the greatest threat to global health and economic security.⁶⁸

The few big pharma companies still participating in the antibiotic market are likely to participate later in the pipeline using market-rate investments. Here corporate or commercial investors invest in a business through equity investments, venture capital, or debt financing. Market-rate investors typically select companies where they feel the opportunity for financial profit is highest.

Post-Market Options

Once an antibiotic has made it through the numerous stages of clinical trials, pull incentives seek to reward the drug's developer by ensuring future revenue. In the antibiotic space, pull incentives have been structured mainly as higher reimbursement models, market exclusivity extensions, market entry rewards, or subscription models. The amount of capital needed for a successful pull incentive is significantly higher than for a push incentive, in part because pull incentives require sustained funding, whereas push incentives

are usually one-time infusions (many of which do not require repayment). Additionally, structuring pull incentives is complicated. They must ensure equal opportunity across high- and low-income countries. There is increased global attention on the need for new market incentive options, as demonstrated by a recent statement by countries of the G7 that included support to pilot and implement pull incentives.⁶⁹

A handful of post-market pull incentives already exist in the market today. One prominent mechanism is a market exclusivity extension. This allows the company to extend the market exclusivity period, essentially delaying the approval of a competing generic product, thus allowing a developer a longer timeline to recoup development and commercialization costs. In the US, under the Generating Antibiotic Incentives Now (GAIN) Act of 2012, antibiotics that are designated a "Qualified Infectious Disease Product" are eligible to receive an additional five years of market exclusivity.⁷⁰ The European Union has also expressed interest in exploring extending market exclusivity through transferable vouchers.⁷¹ Similarly, this mechanism would allow a company to extend market exclusivity of its antibiotic and delay competing generic drugs, except it could be transferred and have its benefit applied to another of its products or sold to another pharmaceutical company for its own drug.⁷² Although this incentive has yet to be implemented, a policy solution was introduced in The Re-Valuing Antimicrobial Products (REVAMP) Act of 2018, but this bill has not been reintroduced.

In addition to the programs mentioned earlier, BARDA has also supported antibiotic development through Project BioShield, which provides a financing source for buying an approved medical countermeasure to promote emergency preparedness and biodefense in the US.⁷³ In 2019, BARDA awarded its first Project BioShield contract for an antibacterial to Paratek Pharmaceuticals for its antibiotic NUZYRA® for use against anthrax infections.⁷⁴ By potentially providing up to \$285 million over a decade, this funding has been instrumental for Paratek to continue developing the product.⁷⁵

A pull mechanism of increasing focus is the reimbursement model. A higher reimbursement structure ensures that antibiotics are priced at a level commensurate with the public health value they provide. Antibiotic reimbursement programs underway in both France and Germany have focused on providing minimum price guarantees.⁷⁶ The programs offer developers downside price protection and minimize the risk that antibiotics will be undervalued. The US has proposed legislation, but a reimbursement model is not yet in effect.

In the US, congressional legislation has been introduced—but not yet passed—that would allow Medicare to provide additional payments to inpatient hospitals for using certain antibiotics. Currently, Medicare reimburses inpatient hospitals a fixed amount for each case (referred to as the DRG system) based on the average cost of an inpatient stay for that diagnosis. Studies have shown that this payment system may discourage hospitals from using newer, costlier antibiotics because they receive the same reimbursement rates as they would for using cheaper alternatives.⁷⁷ The DISARM (Developing an Innovative Strategy for Antimicrobial-Resistant Microorganisms) Act would alter that formula. Under this bill, Medicare would carve out payment for novel antibiotics from existing DRG payments and reimburse them based on their average sales price.⁷⁸

Market-entry rewards are another pull incentive option, consisting of a predetermined payment to antibiotic developers once a product successfully receives market approval and has met a pre-specified target profile.⁷⁹ The payment is separate from and in addition to any revenues from volume sales the developers may receive (this incentive is also referred to as a partially de-linked model).⁸⁰ A variation on the market entry reward is the subscription model, under which an antibiotic developer receives only the predetermined

payment and does not receive any revenues from volume sales (referred to as a fully de-linked model); this model is currently being trialed in the United Kingdom.⁸¹ The subscription incentive guarantees the developer a fixed payment regardless of how often the drug is used.

In addition to encouraging investment in drug development, the subscription model reduces the need to sell large volumes of product, which risks raising resistance levels.⁸² Both market entry rewards and subscription models seek to tie payments to antibiotic developers to the societal value of having that drug available to the public.⁸³ In return, the developer will supply the antibiotic at a volume as required.⁸⁴

The UK and Sweden both have pilot programs underway to test these models, and other countries have shown significant interest in their results. In July 2019, the UK Department of Health and Social Care launched a trial of a subscription model for the payment for antibacterial drugs, the first of its kind. Currently being run in England alone, the goal of the model is to guarantee payment to pharmaceutical companies for access to antibacterial therapies upfront based on their “usefulness” to the British National Health Service (NHS), regardless of the number of doses actually used.⁸⁵ The NHS will negotiate payments of up to £10 million (US\$13.6 million) per drug each year if it meets certain performance criteria, including those on supply availability and good stewardship.⁸⁶ Contracts will generally last for three years but may be extended up to 10.⁸⁷ The maximum fee of £100 million was based on what England considered its “fair share” of the cost of the estimated US\$2 billion to \$4 billion needed globally to support the pipeline.⁸⁸ The model aims to provide a guaranteed revenue to manufacturers, regardless of whether the drug is kept in reserve and not used as regularly.⁸⁹

Measuring Impact through the UK Pilot

The UK subscription pilot is the first of its kind, so the world's eyes are on England to see how it fares. Throughout 2021, Britain's National Institute for Health and Care Excellence (NICE) assessed two novel therapies to determine their "usefulness" to the National Health Service (NHS): cefiderocol (Fetroja) by Shionogi and Pfizer's ceftazidime with avibactam (Zavicefta).⁹⁰ Usefulness was determined not only by a drug's impact on the patients who received it but also by its broader societal value. The findings will help set the subscription payment price for each product, both of which will be available in early 2022.⁹¹

While results were not published at the time of this report, those involved in the pilot commented on the importance placed on measuring impact. The pilot is focused on two main components: evaluating the level of health benefits by quantifying quality-adjusted life years and capturing the broader elements of value (beyond those directly to the patient) provided by new antibiotics. The assumption is that these measurements of value will feed into an agreed payment mechanism to support supply availability and good stewardship. The final evaluation outcomes will inform commercial discussions among payers, government agencies, and suppliers as they negotiate a fixed fee for access to these novel antibiotics, regardless of the number of doses actually used.

Sweden is conducting a similar pilot to the UK but unlike the UK program, the Swedish pilot is based on a market entry reward, or a partially de-linked model. The program aims to ensure that antibiotics of "special medical value" are available in the Swedish market despite protections (such as patents) and low demand that may render the antibiotics unattractive for investors.⁹² The pilot only aims to preserve access; it does not

support R&D.⁹³ Under the trial reimbursement model, the Public Health Agency of Sweden will set a minimum guaranteed annual revenue for each drug, based on an estimate of its safe reserve amount (or "security stock") that is 50 percent above the European average list price. Participating pharmaceutical companies will be required to deliver a predetermined amount of antibiotics within a set period.⁹⁴ If a large volume of sales pushes revenue above this annual payment within a single year, and the company has met its delivery requirement, then it will be paid a bonus equal to 10 percent of what the security stock is worth. These benefits ensure the partially de-linked program is an effective incentive compared to standard volume-based sales.⁹⁵ So far, four companies are participating in the trial—MSD, Shionogi, Pharmaprim, and Unimedica Pharma—with five antibiotics among them.⁹⁶

The US does not currently have a subscription model for antibiotics in place. However, the PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act aims to implement a de-linked subscription model to boost novel antimicrobial development, encourage the appropriate use of existing drugs, and safeguard a domestic supply.⁹⁷ Reintroduced in Congress in 2021 as part of the 21st Century Cures Act 2.0, the bill authorizes guaranteed payments from the federal government to developers ranging between \$750 million to \$3 billion for "unlimited access" to an antibiotic, paid out over five to 10 years.⁹⁸ The budget of the PASTEUR Act would be \$11 billion over 10 years (including \$500 million for stewardship programs), with the goal of financing between three and 14 contracts, depending on their value.⁹⁹

To continue to bring new antibiotics to market, all the programs mentioned will be necessary to build an effective global pull incentive of around \$4 billion estimated for each new antibiotic developed.¹⁰⁰ With that in mind, the Lab convened participants to develop a set of financing recommendations to supplement the existing push and proposed pull incentive options and attract new investors into the antibiotics field.

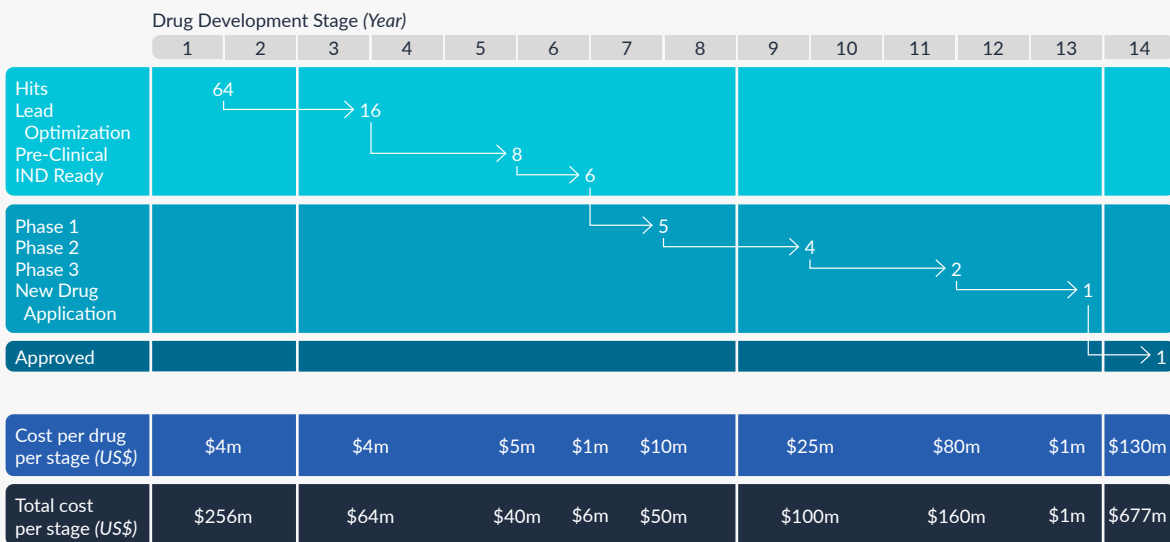
INNOVATIVE FINANCING SOLUTIONS

Discussions at the Financial Innovation Lab focused on identifying options that would attract different types of investors at various stages in the drug development timeline. There was broad agreement that implementing the PASTEUR Act (or other revenue-guaranteeing programs like those being tested in the UK and Sweden) is a critical linchpin, without which most other measures will have limited efficacy. All of the financing recommendations in this report assume that Congress will pass the PASTEUR Act, or relevant government programs elsewhere, and allow federal subscription contract payments to repay investors. Implementation of the PASTEUR Act alone is unlikely to be sufficient to support a robust antibiotic marketplace. A full suite of financing options is necessary.

ESTABLISH A BLENDED CAPITAL FUND

As previously commented, the deeper a drug is in the development pipeline, the less risk associated with investing in it. Lab participants discussed a market example (Figure 3 below) that illustrates how a pipeline with 64 drugs in the preclinical stages is likely to yield only one product that makes it to the commercial market. While scientific risk is reduced year over year, the capital requirements continuously increase, with more than half of costs coming in the last five years of the 14-year process. Even after a drug receives regulatory approval there are ongoing costs for it to achieve its full market potential.

Figure 3: AMR Drug Development Attrition and Costs



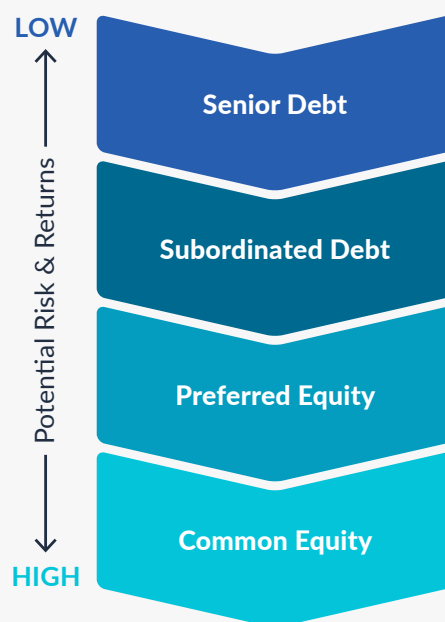
Source: Adapted from INFEX Therapeutics (2021)

These capital needs in the later stages were a key focus for the Lab discussion. Participants with financing expertise pointed out that as products progress through development, different financial tools will be necessary to match the capital needs. Academic, public, and philanthropic grants or concessionary capital will continue to be the lion's share of funding in the earliest stages because the risk of failure is incredibly high. This concessionary capital can also play a meaningful role in the later stages of development by providing first-loss protection, or a guarantee, against a predetermined percentage of loss. But as a business grows and its product is further developed, it typically will add different types of capital to the balance sheet, which is often referred to as a "capital stack." Senior debt is the least risky layer at the top of the stack, as it is the first capital to be repaid in case of default. The other layers in the stack, in increasing order of risk, are subordinated debt, preferred equity, and common equity.

Because each layer appeals to different types of investors, a blended capital fund can be a useful instrument for attracting and capturing a wide pool of potential investors. As an investment vehicle that includes different types of financing (equity or debt), it can adjust to the changing capital needs of a product as it moves through the stages of development. The goal of a blended vehicle is to match company needs more efficiently with investor capital. Such an offering would target financing needs in the late stages of R&D—specifically Phase 2 and Phase 3—with the advantage of widening the pool of investors who may participate.

Investors in the health space are well acquainted with the blended capital structure. The Global Health Investment Fund (GHIF), for example, reduces the risk to traditional investors by absorbing a portion of initial losses. The \$108 million social impact investment fund employs a range of capital options, including various layers of debt investments and equity, with an average investment target of \$10 million per project.¹⁰¹ The Bill & Melinda Gates Foundation provides a first-loss guarantee by absorbing the first 20

Figure 4: The "Capital Stack"



Source: Milken Institute (2022)

percent of potential downside. If an investment loses more than 20 percent, the Gates Foundation splits additional losses 50/50 with the other investors.¹⁰² This structure helps to significantly reduce downside risk, therefore enticing other private capital to participate. The GHIF structure has encouraged philanthropic investors (like the Children's Investment Fund Foundation) as well as traditional investors like AXA Investment Managers, JPMorgan Chase & Co, and the International Finance Corporation to address public health challenges.¹⁰³

Timing of Investment

Initial conversations focused on the timing of capital provided by a blended fund. Flexible capital is most needed in the late stages of Phase 2 and Phase 3 clinical trials. On average, that is 7 to 10 years into a drug's development life, when the amount of capital required increases dramatically. This window is an excellent opportunity to implement a new blended finance solution because the risks and commercialization potential of drugs become reasonably clear as a drug approaches Phase 3 trials and the size of the pull incentive reward becomes visible. The GHIF, for example, targets investment

opportunities that “have a high probability of commercialization within two or three years.”¹⁰⁴ A blended vehicle targeting antibiotic development would likely need to invest with similar return timelines. Therefore, participants felt any investments made into a blended capital fund should target products in the later stages of clinical trials.

Criteria for Qualification

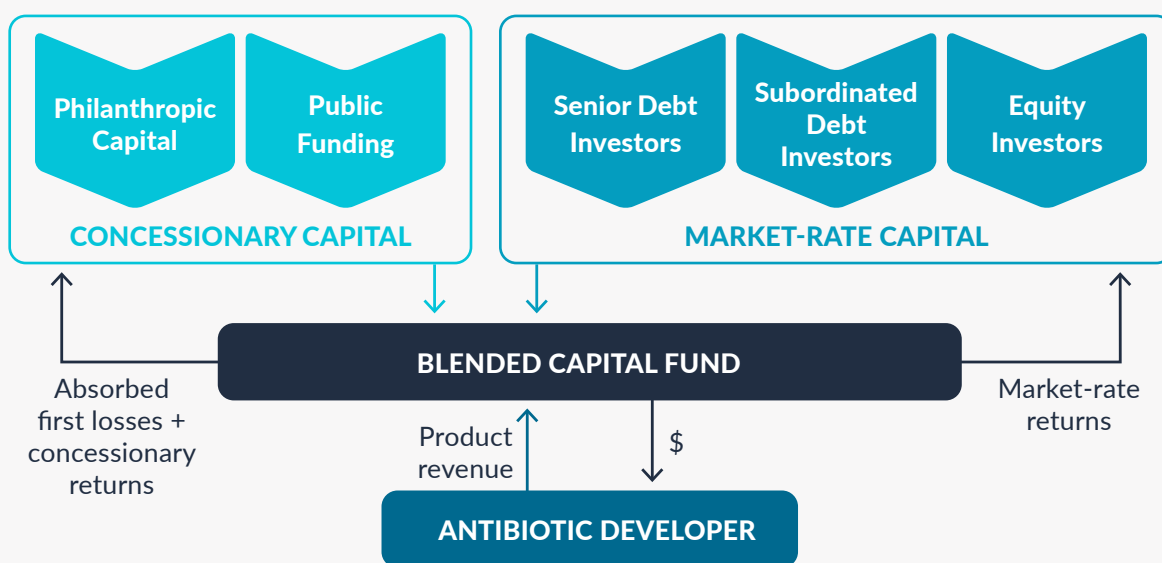
Another critical consideration was how a fund of traditional finance investors would qualify investment opportunities without deep scientific expertise. Lab participants acknowledged that many investors would need a partner to complete the scientific due diligence on antibiotic investment prospects. Outside of sophisticated health-care investment managers, most firms will not have those capabilities in-house. Luckily, the AMR Action Fund, an investment fund backed by numerous pharmaceutical companies and philanthropic organizations (detailed earlier), does have such expertise in the form of a Scientific Advisory Board. The board comprises independent members who can analyze the scientific promise and differentiated clinical utility of new antibiotic candidates identified to combat

priority pathogens. Lab participants discussed the benefit and synergies of having private market blended capital available to invest alongside drugs vetted by the AMR Action Fund in earlier stages of development.

Return Expectations

While many public and philanthropic investors participate early in the pipeline, concessionary capital plays an important role even in the later stages. It can be used to reduce risk to private investors, encouraging them to participate in the market earlier than they otherwise would feel comfortable. Participants discussed incorporating a sliding first loss or guarantee into the structure of a blended capital fund. While the fund should target clinical Phases 2 and Phase 3, the risk level is different at each stage, hence the need for a sliding scale. Sliding first-loss protection would guarantee against a higher percentage of downside for investors participating in earlier phases, compared to those in the later ones when some of the scientific and commercialization risks have been reduced. Traditional investors willing to invest as early as Phase 2 would likely need first-loss protection as high as 50 percent. The first-loss protection would “slide” down to 20 percent as the antibiotic moves into later clinical phases.

Figure 5: Blended Capital Fund Model



Source: Milken Institute (2022)

The risks for a Phase 2 or Phase 3 drug are less technical and primarily related to commercialization. To reduce commercialization risk as much as possible, Lab participants suggested any drugs for investment consideration should be prequalified for a PASTEUR contract (as is proposed within the bill), a UK incentive, or other quasi-market guarantee. Doing so would guarantee a return to lower-risk investors if the drug receives regulatory approval. Given the risk-return profile of such an investment, Lab participants felt return expectations in the high single digits to the low teens were realistic. For reference, the GHIF targets returns of 5 to 7 percent for its investors.¹⁰⁵

Fund Size

The AMR Action Fund aims to invest \$1 billion in hopes of developing two to four new antibiotics. Lab participants agreed that the sweet spot for a blended capital vehicle would leverage that amount by a factor of 2-3x (i.e., \$2 billion to \$3 billion). However, given the novelty of such a vehicle, participants acknowledged a more realistic starting goal might be closer to \$300 million, or three times the size of the GHIF.¹⁰⁶ Diversification was an area of concern because the antibiotic pipeline may not be robust enough in size to allow for the spreading of risk. Some Lab participants likened antibiotic diversification to the various methodologies

used to develop COVID-19 vaccines. While all COVID-19 vaccine manufacturers target the same pathogen, the scientific approach could diversify a portfolio of investments. Participants agreed that a blended capital antibiotic portfolio would need to invest in at least 10 products in various development stages or use different methodologies to diversify risk enough for a traditional private institutional investor.

Measuring Impact

To attract market-rate impact and concessionary investors, it is essential to be able to measure and assess the effects of various interventions. In recent years, stakeholders in the antibiotic market have realized the importance of measuring the global need for new drugs and have worked to quantify the gaps in the pipeline. Lab participants discussed key metrics to measure against, such as the cost of meeting unmet health-care needs, the rising level of drug-resistant pathogens, and the overall societal benefit of effective antibiotics. Much of these data sets can be gathered during the clinical trial process. However, participants acknowledged this requires drug manufacturers to consider risk management. Investors and other capital providers need to promote scientific risk-taking early on to ensure novel drugs are being introduced to the market.

NEXT STEPS

- Identify and encourage investors, including foundations, impact investors, and philanthropic entities willing to provide concessionary capital. These stakeholders must be identified first in order to iron out the structuring of the first-loss component.
- Establish a partnership with the AMR Action Fund Scientific Advisory Board to analyze investment opportunities and establish the criteria for qualification.
- Outline metrics to measure and assess social impact.

POOL DRUG ASSETS INTO A BOND STRUCTURE

The uncertainty associated with drug development up to Phase 3 limits funding sources to investors with relatively high-risk appetites. But as an antibiotic reaches the regulatory approval phase, the technical risk is reduced significantly. Throughout the Lab process, participants likened antibiotics to the infrastructure of the health-care system. The same way investments in infrastructure modernize society, investments in antibiotics modernize and adapt to today's health-care system. Traditional infrastructure is often financed through bonds. Bonds are issued to raise upfront financing to build a bridge or tunnel, and investors are repaid (at a predetermined interest rate) at regular intervals over a period of years. Investors are attracted to infrastructure investments because they earn a modest but steady return at a reduced risk over a defined period.

While a successful oncology drug may earn venture-capital-like returns, antibiotics are much more aligned to the timelines and return expectations of an infrastructure investment. To attract new pools of capital, Lab participants discussed options to combine a portion of the revenue of a handful of underlying drug assets into a single sellable security, a process known as securitization. This securitized bond structure would invest in the post-market stages of the pipeline based on the monetization of a PASTEUR-like contract.

While a securitized loan vehicle based on future contracts has not been specifically applied to financing antibiotic development before, Royalty Pharma has recently turned to future revenue to support late-stage drug development. Royalty Pharma's business model provides low-cost funding to drug developers to help push promising products through clinical trials. In return, the fund negotiates "a predetermined slice of that drug's revenue in the years after it reaches the market."¹⁰⁷ Since the financing is provided only for late-stage deals, Royalty Pharma typically has good sightlines to commercialization. From 2012 to 2020, 90

percent of the drugs the fund invested in achieved regulatory approval.¹⁰⁸ In June 2021, Royalty Pharma announced a creative financing structure with MorphoSys, a German biopharmaceutical company. The financing has a few layers, including equity and milestone payments, but notably, it includes "access to \$350 million in development funding bonds," which MorphoSys can "draw over a 1-year period at a minimum of \$150 million."¹⁰⁹ Royalty Pharma's strong track record in creative financing signals to the market that fixed-income instruments can be used to finance late-stage and post-market drug development.

Timing of Investment

Lab participants considered how early in the R&D process it was possible to attach a value to the future subscription contracts. Discussions centered on the benefit of a "prequalification" acknowledgment for a promising antibiotic, even as early as Phase 1, before the drug has received full regulatory approval. This early signal would allow the market to project future revenues (in the form of subscription payments) and gain clarity on potential return expectations of a bond structure. Like Royalty Pharma's investment thesis, a pooled asset structure financed through bonds is likely only a viable option in the later or post-market stages of the development pipeline. But a "prequalification" acknowledgment could allow investors to be comfortable making a slightly earlier investment than they otherwise would. The premise of the design is to securitize the government subscription contracts, so the timing of the investment payouts must align with the government issuing of payments.

Criteria for Qualification

Building on the idea of antibiotics as the infrastructure of the health-care system, Lab participants designed an "antibiotic bond" in which the committed subscription payments from a PASTEUR contract would provide the capital to pay back investors. An antibiotic approved by PASTEUR

will have defined contract payments for up to 10 years, as outlined in the current bill, reducing the commercial risk and providing a similar payback timeline for a typical infrastructure investment.

The initial step to pooling together a group of antibiotic drug assets is building protections against bankruptcy risk. The revenue-producing asset—in this case, the antibiotic approved to receive PASTEUR subscription payments, as well as the rights to future cash flows generated by the asset—should not be directly owned by an operating company that is at risk of going bankrupt. Reducing this risk is particularly critical because many of the underlying assets are likely to be produced and owned by small- to medium-sized enterprise developers. To preclude this from happening, each company would need to assign each asset (including the intellectual property protecting the asset and rights to future cash flows to be generated by the asset) to a bankruptcy-remote special purpose vehicle (SPV). This can usually be done on a tax-free basis and will satisfy the threshold requirement for receiving an investment-grade rating of the security to be issued by the SPV. Assuming each biotech continues to develop its transferred asset, it will be necessary to establish seller-manager agreements with the SPV and bond trustee. If any of the pooled assets earn additional revenue outside of the subscription contracts, the seller-manager agreements will outline the use of proceeds.

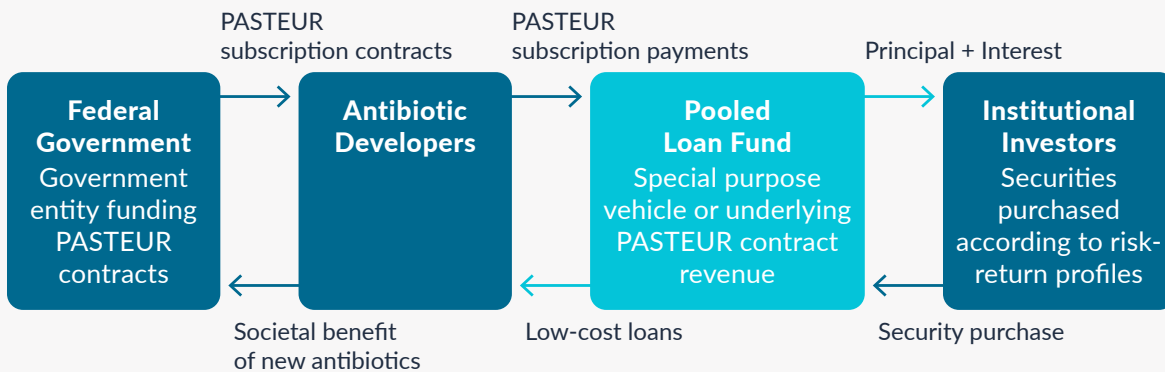
Once the underlying antibiotics are pooled, rating agencies must predict the cash flows of the assets collateralizing the security. Since each underlying asset will have been approved contractually for PASTEUR payments from the federal government, rating agencies should be able to make conservative annual assumptions about production and delivery, allowing them to estimate cash flows. As with any type of agreement, the risk of termination due to unforeseen issues, such as fraud, negligence, or failure to meet certain performance standards, cannot be ignored.

These risks would be addressed primarily through (a) due diligence completed ahead of any bond being issued and (b) trigger mechanisms included in the bond documents that permit the replacement of the seller-manager with either a new substitute seller-manager or with a master collateral manager. For context, to receive a single-A bond rating, the security must have less than a 1 percent probability of default over the lifetime of the issuance. Given the financial markets have never valued these types of contracts before, this model could serve as a pilot for others; the existence of the PASTEUR contractual backstop will enhance the ability of the bonds to be rated investment grade over what would be the case without such credit support.

It is essential, therefore, that PASTEUR's government contracts are structured in a way that allows private investors to receive a financial return. As the revenue for this model is dependent on federal subscription payments, giving investors financial certainty will require eliminating political risk. Any ambiguity around whether the subscription payments can be changed or canceled before the end of the agreed term makes the structure too risky for investors. Long-term funding settlement language must be written into the structure of the subscription payments to eliminate the potential for funding to change before the end of the bond term.

Equally important to include in the legislation is a clear set of metrics and criteria on which antibiotics will be evaluated and on which payments under the PASTEUR contracts will be made. This will allow antibiotic developers to understand how their products will be assessed and how to measure the government credit support. The UK pilot program underway has been very transparent on the metrics they are looking for. This type of transparency will require coordination between existing government-funded push mechanisms and this innovative pull mechanism to give investors the confidence to put their capital to work alongside public funding.

Figure 6: Pooled Loan Model



Source: Milken Institute (2022)

Return Expectations

An “antibiotic bond” would issue debt to raise money from fixed-income investors. The guaranteed PASTEUR contracts would determine the principal amounts and expected yields. Investors would earn a low single-digit return to be paid from the guaranteed federal government contracts and any revenue generated from international market distribution. Under this model, the federal government would be the counterparty paying the committed contracts, enticing investors by reducing risk.

Pooled Vehicle Size

Ultimately, the size of the securitized instrument will depend on the value of the PASTEUR contract awarded to each asset. As with the blended capital fund, diversification of the underlying assets is key. There are three risk categories that must be addressed: market risk (which incorporates commercialization risk), reimbursement/competition risk, and scientific risk. The PASTEUR contracts address the first two; the structure does not address scientific risk, but it can be mitigated through diversification. Lab participants suggested using various diversification screens, such as selecting drugs that attack different bacteria, use multiple scientific methods (as in the case of the C-19 vaccines), or are at different phases of development. In a portfolio of post-approved drugs, the group felt as few as six underlying antibiotics

could be enough. However, the more certain the payments are under the federal PASTEUR contracts, the less dependent the bond will be on diversification of a non-correlated asset pool. The contracts for each antibiotic could range from \$750 million to \$3 billion, according to the proposed legislation.

With any pooled vehicle, the highest priority is for the assets to have a low correlation with one another. In most cases, a portfolio of antibiotics would be too correlated because the drugs would be fighting for a similar market share once commercialized. However, the PASTEUR contracts help eliminate that issue since each underlying drug would be pre-approved for its own guaranteed subscription payments and therefore not cannibalize another’s market share. As noted above, the primary need for diversification is to mitigate scientific risk. Other structuring considerations would include implementing safeguards around an alignment of interest or backstop if the primary sponsor fails, plus the mechanism for replacing the seller-manager as discussed above.

Measuring Impact

Investors of all types and sizes are increasingly looking for creative investment opportunities to meet their ever-growing environmental, social, and governance (ESG) mandates. A securitized vehicle

to finance the development of novel antibiotics is exactly the kind of product that could appeal to socially conscious investors. To date, however, no one in the financial markets has formally made a case for combating antimicrobial resistance as an environmental or social good. The Sustainability Accounting Standards Board (which sets standards for what counts as sustainable investing) considers antibiotic use in animal production one of its criteria for investing in biotechnology and pharmaceuticals, but does not specifically mention the societal value of maintaining a robust antibiotic pipeline.¹¹⁰ As regions like the EU discuss a taxonomy to define what types of investments can be classified as sustainable, antibiotic risk must be included in the do-no-harm criteria. To that end, the industry needs to communicate the impacts of antibiotics and antimicrobial resistance on both the state of world health and the global economy.

There are a handful of frameworks and standards that traditional ESG investors typically use to

assess and measure investment opportunities. As more of the market is turning to these established frameworks like the Sustainability Accounting Standards Board, the UN's Sustainable Development Goals, the Global Reporting Initiative, and the Taskforce on Climate-related Financial Disclosures, to name a few, the risks of a diminishing antibiotic pipeline must be a factor of consideration. For example, participants recommended that each of the prominent ESG frameworks must integrate the insurance value of a strong pipeline to ensure the risk be more widely discussed by the investment community.

Under the UK subscription plan and the proposed PASTEUR legislation, products must meet a high unmet demand to receive funding. Criteria for measuring a drug's sustainability should include data about its novelty, the severity of the situation it seeks to remedy, and the company's track record related to manufacturing, surveillance, and stewardship.

NEXT STEPS:

- Communicate the health and economic impacts of antibiotics and antimicrobial resistance to attract investors looking for sustainable investment opportunities.
- Consult with one or more investment banks to obtain feedback on the marketability of the proposed bonds.
- Define the criteria for antibiotics to be considered for inclusion, ensuring diversification of the underlying assets.
- Transfer qualifying antibiotic assets into a dedicated special purpose vehicle to reduce bankruptcy risk.
- Incorporate rating agencies into the structuring process to assess the risk associated with the cash flows from the government subscription contracts. Lessons can be learned from the early days of structuring residential solar assets, where bonds were assigned hypothetical rating proposals in the form of legal structures, term sheets, and simulated asset pools. This would allow for feedback to be incorporated before rating agencies are asked to issue "real" ratings on an actual transaction.



CONCLUSION

Antimicrobial resistance and the waning arsenal of drugs the world has to fight bacterial infections are issues of global concern. But funding for these essential tools has been stretched beyond the point of being sustainable. It is crucial, therefore, to harness every opportunity to reduce investor risk and increase the size of the antibiotic pipeline. Government and philanthropic capital will continue to play a leading role in moving antibiotics from the science lab into clinical trials. But as products successfully track through the various clinical stages, innovative financing structures such as a blended capital fund could allocate available resources more efficiently while attracting new investor types. And once a drug is ready for the market, securitizing subscription contracts into a bond model to remunerate developers will further entice private investors to address this public health crisis.

To advance either of the financing model recommendations at the scale required to address the market challenges will take a multi-industry effort. The dedicated AMR experts who have been actively funding antibiotics through many of the programs previously mentioned can provide invaluable guidance around the nuances of antibiotics to help ensure the structure of the funds are feasible and useful. Government leaders working on federal subscription programs must be transparent around qualifying guidelines and flexible and responsive to market feedback to develop a program that will be successful with the intended benefits. And finally, the investor and big pharma communities have critical roles to play by calculating the financial risks associated with allowing the antibiotic R&D pipeline to fail. A lack of concerted effort by any one party will handicap a successful intervention.

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