MILKEN INSTITUTE

Financial Innovations Lab®

Executive Summary: Models for Financing Antibiotic Development to Address Antimicrobial Resistance

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. In 2019, as many as 1.27 million deaths globally were directly attributable to AMR, according to a recent study.[1] 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.[2] The development and successful commercialization of novel antibiotics are thus vital to maintaining the very foundation of a healthy and operational society, one that is prepared for future public health pandemics.

A comprehensive public health preparedness and response system must integrate planning for all pandemic sources, including AMR. New antibiotics are crucial not only to curbing resistance but also to responding to future public health emergencies, which, like COVID-19, may carry a significant risk of hospitalization and secondary bacterial infections. The threat of allowing our arsenal of antibiotic defenses to lapse is well documented, and addressing the issue is essential to strengthening pandemic preparedness capabilities for public health concerns in the future. Although more analyses must be done to determine the specific role and impact secondary bacterial infections have on COVID-19 mortality, current studies have found a higher incidence of bacterial infections in fatal cases as compared to recovered cases.[3] Without the necessary incentives and financing instruments to encourage private investment in antibiotic innovation, the future of global health is ominous.

In 2021, the Milken Institute organized a Financial Innovations Lab project in collaboration with Wellcome Trust to explore innovative financing models to foster investment in novel antibiotics. Through months of research, stakeholder interviews, and group convenings, the Institute 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 to innovate new financing structures. During a Lab workshop held in September, participants identified two key financing mechanisms that could drive new forms of capital to antibiotic development:

- 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 given antibiotics' likeness to a traditional infrastructure investment's return and timeline expectations. Participants designed an 'antibiotic bond' in which the committed subscription payments from a PASTEUR contract would provide the capital to pay back investors.

Participants agreed there must be a federal government guarantee to address antibiotic development to move either idea forward. Therefore, the models assume and integrate financing provided from the proposed PASTEUR Act in the US and other revenue-guaranteeing programs globally.

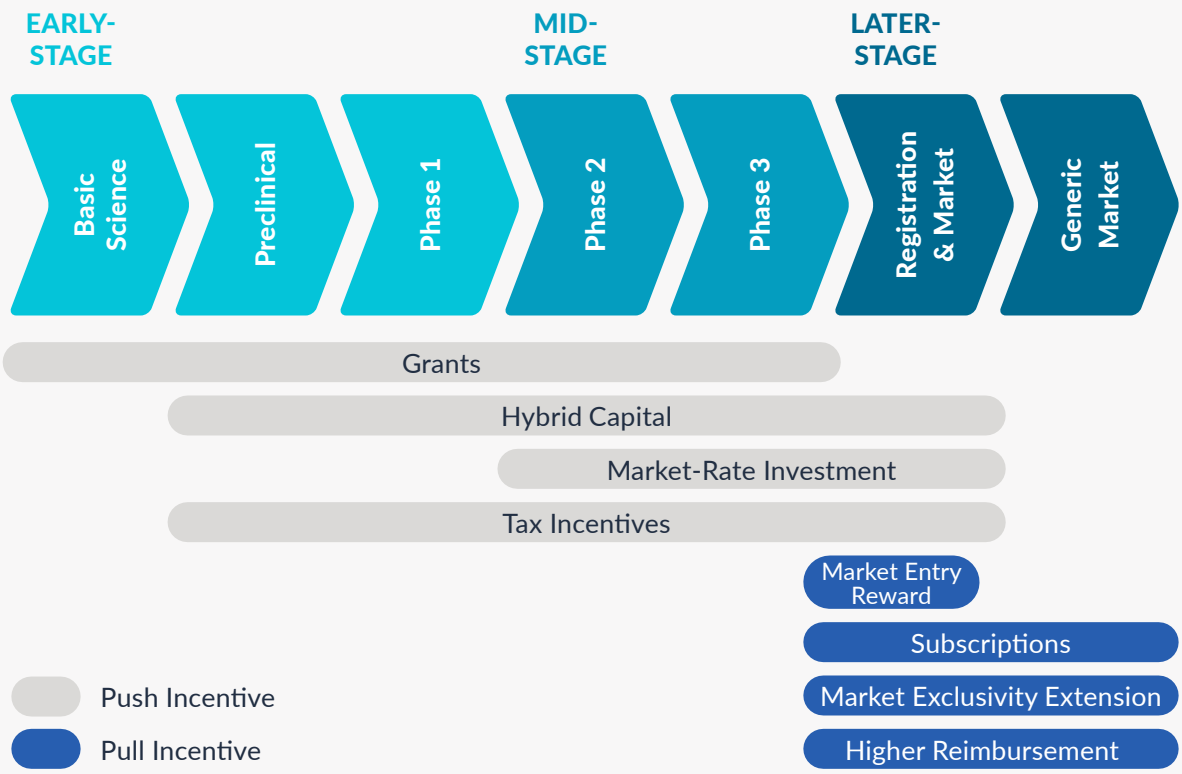
ISSUES AND PERSPECTIVES

All stakeholders play a role in combatting resistance and creating a landscape conducive to sustainable antibiotic development. For clinical participants, this means sharing the responsibility of antibiotic stewardship, as 65 percent of doctors recognize increasing resistance yet do not view themselves as directly involved in the problem.[4] On the financing front, an estimated $1.2 billion must enter the market every year[5] to support antibiotic innovation—a burden that could be eased by addressing the market's current failures so that private investment is more willing to participate. Without the promise of financial returns, many pharmaceutical companies have also exited the antibiotic market, leaving innovation up to SME biotech companies that are even more reliant on external financing compared to their large multinational peers.

Antibiotic development is time- and capital-intensive, spanning upwards of a decade and with cumulative costs frequently exceeding $1 billion.[6] With other categories of drugs, the development costs are typically recouped once a drug reaches the market through commercial revenue. However, this volume-based business model is incompatible with antibiotics since antibiotics are intended to be used sparingly. The high development costs and reduced possibility of revenue generation have deterred investors from financing antibiotic R&D, which has led to an insufficient pipeline.

A balance of different financial incentives to encourage investment is needed across the R&D timeline—and are typically described as either push or pull incentives. Push incentives target capital needs for early R&D, while pull incentives seek to provide a future revenue stream for later-stage approved products. Early-stage antibiotic development and push incentives are primarily funded through public or philanthropic money without repayment expectations. In contrast, late-stage development is driven by hybrid capital such as venture philanthropy, recoverable grants, and below-market-rate investments. Once the product makes it to market, pull incentives come into play. These can take the form of higher reimbursement, market exclusivity extensions, market entry rewards, or subscription payments, such as those described in the PASTEUR Act. Restructuring payment models for antibiotics in this way, in tandem with the funding options recommended by Lab participants, will be vital to reach the estimated investments.[7]

Figure 1: Antibiotic Funding Options by Stage



Source: *Milken Institute (2022)*

INNOVATIVE FINANCING SOLUTIONS

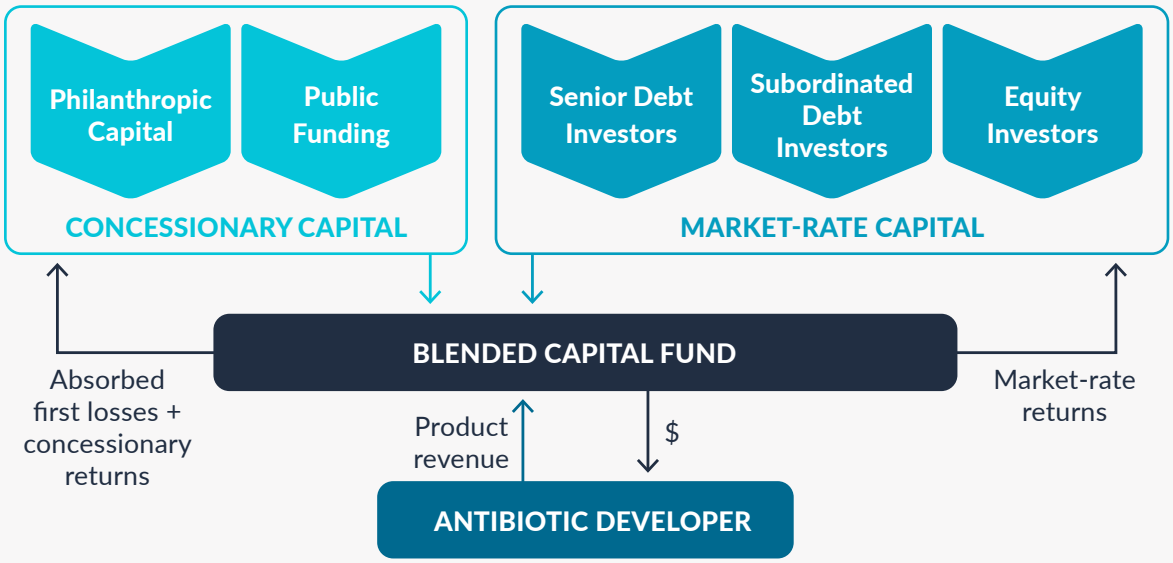
Discussions at the Financial Innovations Lab focused on identifying options that would attract diverse types of investors at various stages in the drug development timeline. Lab participants agreed that the PASTEUR Act is not sufficient alone, and the utility of other financing options relies on its implementation. Therefore, the financing recommendations outlined in this summary assume that Congress will pass this program or a similar revenue-guaranteeing subscription mechanism.

ESTABLISH A BLENDED CAPITAL FUND

The earliest stages of drug development are typically funded by public and philanthropic concessionary capital as the risk of failure is highest. As the drug advances through to the later stages of development, diverse funding sources start to contribute. This layered financing is often referred to as a "capital stack," with senior debt at the top to be repaid first followed by higher risk, higher return options such as subordinated debt, preferred equity, and common equity. As each layer appeals to a different type of investor, introducing a blended capital investment fund to the antibiotic market will expand the pool of potential investors. A fund of this type will be able to match assets to the right financing across all stages of an antibiotic's life cycle according to the asset's varying capital needs and different investors' risk-return profiles.

A blended capital fund is particularly advantageous for the later stages of clinical trials, or Phases 2 and 3, where flexible capital is most needed, and the risks and revenue potential of the drug become clearer. While the fund should target Phases 2 and 3, risk can vary at each stage, so Lab participants suggested incorporating a sliding first loss or guarantee into the blended capital structure. Additionally, commercialization risk can be tempered by only selecting for drugs that have prequalified for a proposed PASTEUR contract, a UK incentive, or other quasi-market guarantees so that lower-risk investors will receive a return if regulatory approval is granted.

Figure 2: Blended Capital Fund Model



Source: Milken Institute (2022)

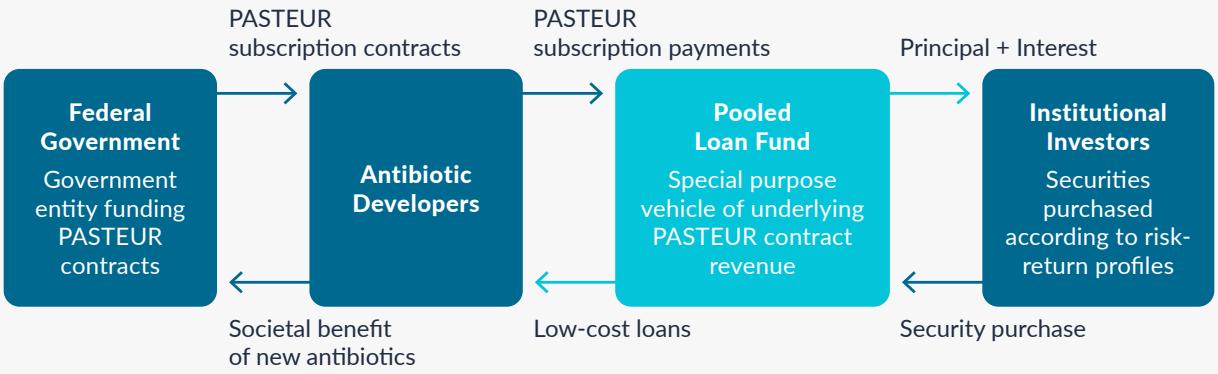
A real-world application of the blended capital model is the Global Health Investment Fund (GHIF), a $108 million social impact fund of different types of debt and equity and a first loss guarantee.[8] Using the GHIF's size as a launchpad, Lab participants agreed that a fund three times its size, at $300 million, would be a realistic starting point. To diversify portfolio risk for private investors further, the fund would invest in at least 10 products of varying methodology or development stages. Drug manufacturers could also appeal to the broad pool of market-rate impact and concessionary investors by reporting on risk management metrics that quantify the social impact. That is often an important consideration for concessionary investors when selecting opportunities.

POOL DRUG ASSETS INTO A BOND STRUCTURE

Throughout the Lab process, participants likened antibiotics to the infrastructure of the health-care system. Likewise, the antibiotic development timeline and return expectations mirror those of traditional infrastructure investments. Infrastructure investments often attract risk-averse investors as they are typically lower risk and earn consistent returns over a predetermined period. An investment structure of that type would be valuable in the antibiotic market, which has uncertain returns, if any, and requires patient capital. This "antibiotic bond," as coined by Lab participants, would issue debt to raise money from the likes of traditional fixed-income investors. The functionality of this bond is contingent on creating a revenue-guaranteeing mechanism, where the revenue would serve as the bond's guaranteed repayment.

Although not yet passed in the US Congress, the PASTEUR Act is a proposed bill that would guarantee revenue via federal subscription contract payments made to developers ranging from $750 million to $3 billion for access to approved antibiotics.[9] Lab participants discussed bundling a portion of this guaranteed revenue from a diversified group of underlying antibiotics and repackaging them into a single asset to entice new capital sources, a process known as securitization. With the federal government committing the subscription contract payments, the counterparty risk to investors would be reduced. Furthermore, diversification of the included antibiotics will protect against any uncorrelated risk. The securitized loan vehicle would then invest in the post-market development process based on the monetization of a PASTEUR-like contract.

Figure 3: Pooled Loan Model



Source: Milken Institute (2022)

Lab participants highlighted the importance of incorporating long-term funding settlement language into the subscription payment framework to further reassure private investors of their expected financial return. This is a crucial factor because it would protect against any potential for funding modifications throughout the bond term. For antibiotic developers, the legislation should outline expectations for which types of antibiotics will be evaluated and by what metrics the PASTEUR contracts will be granted, so that antibiotic developers understand how products will be considered. Ultimately, the size of the securitized "antibiotic bond" will depend on the underlying value of the subscription contracts given to each asset. While this PASTEUR funding addresses the assets' market and reimbursement risk, the instrument's scientific risk would be reduced through diversification and selecting assets with low correlation, mitigating any fear of competing market share.

As the market for social impact capital grows, the antibiotic development community should respond by articulating the economic and life-saving societal gains from a securitized vehicle like this. As the PASTEUR Act is developed further, the associated investment opportunities should be considered sustainable investments under an established ESG framework. Doing so would appeal to impact investors searching for new opportunities, especially one that may better prepare us for future pandemics.

CONCLUSION AND NEXT STEPS

As antimicrobial resistance increases and once-treatable bacterial infections become life-threatening, the need to repair our antibiotic funding model has never been more critical. Although government and philanthropic capital will continue to play an outsized role in advancing antibiotics from the discovery lab into clinical trials, innovative financing structures such as a blended capital model would attract new pools of investors and efficiently match capital to individual risk. Private investment can continue to take on a greater role once a drug reaches the market via participation in an "antibiotic bond" that uses PASTEUR subscription payments to pay back investors.

All stakeholders, fulfilling their respective roles in the fight against AMR, collectively have the potential to prevent this silent pandemic from continuing down its destructive path. AMR researchers can lend their expertise in the current landscape to work with funding entities to construct the most beneficial and viable financing options. Government leaders should integrate the capital market perspective to establish federal subscription programs. Subscription programs, such as the PASTEUR Act, must prioritize transparency around qualifying guidelines and the flexibility to adapt as needed. Finally, investors and drug manufacturers must put risk management into practice by creating metrics to quantify the social and financial consequences of a crumbling antibiotic pipeline—or else risk having it render the rest of our pandemic preparedness and response strategies futile.

The Milken Institute will continue its work to address the capital challenges around antibiotic R&D. With the basic components of new financing models designed, next steps will include focused conversations around the structuring and implementation of the recommendations. The Institute will also continue to advocate for incentives to encourage antibiotic development, including the PASTEUR Act in the US, and urge policymakers to integrate AMR into pandemic preparedness strategies.

View the full report at: ***https://milkeninstitute.org/report/antimicrobial-resistance-antibiotic-development***

ENDNOTES

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