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Antimicrobial resistance (AMR) is a growing threat to global health and wealth. Although new antibiotics are needed to address AMR, industry investment in new antibiotics is limited, due to the expected low economic returns on these projects. The UK implemented a $13M pull incentive in 2022, to provide additional funds to motivate private sector actors to invest in new antibiotics and stakeholders have suggested other OECD governments join these efforts. We examine how large an incentive for industry is needed to invest in new antibiotics to address AMR, using a model of economic return based on Internal Rate of Return (IRR) measures and incorporating the latest data on development phase progression and costs. To achieve a minimum IRR of 11%, our results suggest a government funded market entry reward on the order of $2.6 billion, paid over ten years, would be required to incentivize the development of one new antimicrobial agent. If six new antibiotics were required over a period of ten years, the total indicated fund would be $15.6 billion. Compared to the direct and indirect costs of doing nothing, our estimated cost of a pull incentive seems manageable, and is consistent with estimates of an AMR pull incentive recently proposed in the US Pasteur Act (up to $3 billion). Our estimates provide a foundation for governments and potentially other stakeholders to pursue the development of new antibiotics to avoid or mitigate the AMR crisis.

Introduction

The development and commercialization of antibiotics has been one of the most dramatic success stories of modern medicine. By mitigating the previous lethal risks associated with many communicable infections, antibiotic-based therapy has allowed life expectancies worldwide to increase by some thirty years over the last century.[i] Unfortunately, the effectiveness of the existing antibiotic armamentarium is decreasing, as pathogens become increasingly resistant to existing medicines, a result of selective pressures in an environment of widespread antibiotic usage. In recent years, antibiotic-resistant infections have become a leading cause of death in U.S. hospitals and worldwide.[ii] Addressing antimicrobial resistance (AMR) also imposes costs on health systems. A 2023 report estimated projected levels of AMR could cost $29 billion per year up to 2050 for 34 OECD countries[iii]. AMR could also cause a total economic loss of $36.9 billion per year across the 34 countries, caused by reduced workforce participation and productivity. Thus, the development of novel medicines, among other approaches, is critical to treat today's antibiotic-resistant infections and to prepare for future threats.

New medicines are generally commercialized by private companies, however OECD governments, especially the US and UK/European Union member countries, play a significant supportive role in innovation through regulation, tax policy, and coverage and reimbursement after approval[iv]. Government grants support basic research into fundamental biological phenomena, in academic institutions and small businesses, and also fund more "translational" development of promising commercial products. Venture capital (VC) will finance high-risk early-stage start-ups that, if successful, will be acquired by large pharmaceutical companies with the substantial resources in sales, distribution, and marketing required to commercialize the product[v]. The venture investment may be internal funding by a large pharmaceutical company rather than by a private VC firm, or the "exit" by the VC equity-owner can be via an Initial Public Offering, rather than via sale to a corporate acquirer. Irrespective of the form of exit, economic value is created along this entire pathway, where participants realize a portion of the full return on investment.

While the development of new antibiotics was a focus by private companies for several decades in the twentieth century, pharmaceutical companies and their funders have, for the most part, lost interest in developing and commercializing novel antibiotics[vi], [vii]. As recently as 1990, there were 18 major pharmaceutical companies actively engaged in bringing new antibiotics to market; yet by 2020, there were only six major pharmaceutical companies with dedicated antibiotic drug development teams.[viii] According to the most recent (2022) World Health Organization (WHO) Pipeline Report, there are only 77 antimicrobial projects in the clinical pipeline, and only 27 of those address what the WHO calls "priority pathogens" where the need is greatest, due to multi-drug resistance or other factors.[ix] By contrast, oncology has over 5,000 trials ongoing currently, just in Phases 1 and 2, and another nearly 1,000 in Phase 3.[x]

Poor economics drives lack of novel antibiotic development and commercialization

Economics drives the pharmaceutical industry's loss of interest; there is simply not enough annual or lifetime revenue during the patent term expected from the development of a new

antibiotic to earn a good return relative to other opportunities for investment in drugs to treat autoimmune disease, heart disease and related conditions or cancer[xi], [xii], [xiii]. A recent report estimated the average global annual revenue for new antibiotic drugs launched between 2010 and 2020 was $46 million, the median annual revenue amounted to only $16 million, and the cumulative revenue for all drugs was $714.3 million (all sales numbers are unadjusted for inflation).[xiv] This suggests the sales of novel antibiotics combined over the first decade of their availability will not amount to the sales of one blockbuster drug in a given year. In contrast, in the first decade after launch, Humira, an anti-inflammatory drug launched in 2003, had cumulative sales amounting to $62 billion, Crestor, a cholesterol lowering agent launched in 2001, had cumulative sales of $41.8 billion, and Avastin, an antiangiogenic agent used in cancer treatment and launched in 2006, had cumulative sales of $49 billion (all sales numbers are unadjusted for inflation). The US is the largest single market for pharmaceuticals and would likely be the main source of revenue for new antibiotics. We analyzed the ten largest selling antibiotics, including brands and generics, in the US in 2022 and across all they have less than $2 billion in aggregate annual revenue (Table 1)..

Table 1. Top Selling Antibiotics in the U.S. (2022)

Antibiotic Agent	Manufacturer	Annual Revenue
1. Zosyn	Pfizer	$256.6 million
2. Amoxicillin	generic	213.2
3. Vancomycin	generic	195.4
4. Penicillin G	generic	161.2
5. Dalbavancin	Durata	149.8
6. Doxycycline	generic	149.7
7. Tobramycin	generic	136.2
8. Avycaz	Allergan/Pfizer	126.7
9. Azithromycin	generic	119.7
10. Teflaro	Allergan	116.5

Source: Authors analysis of IQVIA U.S. National Sales Perspectives, 2022

Rationales for poor economic performance of novel antibiotics

There are several likely rationales that underlie the modest revenues we observe among brand antibiotics, relative to other medicines. First, in the US and globally, the majority of antibiotic volume is old, off-patent (generic), low-priced products, which work reasonably well most of the time. According to our analysis of US pharmaceutical sales, generic antibiotics are top selling products (Table 1). Global statistics also suggest generic antibiotics now account for the majority of spendings on antibiotics, while the on-patent antibiotics market is shrinking; global revenues for on-patent antibiotics fell from $19 Billion in 1999 to $8 Billion in 2021.[xv] Payers and various state laws in the US and the OECD prefer the use of generics whenever available over the use of brands. Therefore, any new on-patent product would have to compete with a market that would be heavily tilted away from their use. Furthermore, since new antibiotics are typically approved

in non-inferiority trials, they do not demonstrate the clinical superiority that might drive adoption.

Second, both in the US and UK/EU, new antibiotics are commonly subject to payer rules that cap the prices which can be set by drug makers[xvi]. Many antibiotics approved for sale in the US in the last ten years are intended primarily for inpatient hospital use. Antibiotics used in the inpatient setting are subject to reimbursement rules that are based on the complete bundle of services that the hospital provides, including physician time, procedures, diagnostics and drugs. This contrasts with many other drugs that are reimbursed separately, and priced accordingly.

Third, the duration of treatment with an antibiotic drug is typically brief (3-21 days)[xvii], compared with the potential for months or years of use of a cancer drug, or the lifetime use of a diabetes or immunology drug. Recent studies even show that "shorter is better" in the case of antibacterial treatment[xviii].

Fourth, and perhaps most importantly, stewardship demands that any novel and effective antibiotic be held in reserve – that is, only used as a last resort in cases that have not responded to conventional treatment[xix], [xx]. This is to guard against resistance developing to the last line of defense. In other words, if a new antibiotic were brought to market, good medical practice would dictate it remain generally unused, except in crisis, even if (rather *especially* if) it was shown to be far superior clinically to existing products. In this case, expected sales volume and revenue would be very low, or even zero, if the "last resort" was not employed.

The result of modest revenue potential is that while there has been some VC investment in antibiotic development in recent years, the amounts are modest, and innovating companies are challenged to find capital. Over the past decade, total VC funding for antibiotics has stalled at less than $200 million yearly[xxi] (less than 1% of biotech venture funding), while venture funding more generally has expanded rapidly. In contrast, oncology venture funding has grown from $800 million ten years ago to $6.4 billion in 2021.[xxii] At least 80% of prospective new antibiotic agents are developed at small VC-backed companies, not at big pharma.[xxiii] The fate of many of these VC-backed companies is not promising, which likely leads to less interest. A Biotechnology Innovation Organization study established that of the 12 antibiotics companies that have gone public over the last decade, only 5 are still active today.[xxiv]

Proposed solutions to challenges in the development of new antibiotics

To address the missing market for novel antibiotics to address the AMR threat, economic incentives have been proposed or implemented that may be classified into either of two types. First, push incentive programs provide financial support for research and development activities, in advance of and independent of the success of the prospective medicine. Several push incentive programs have been created to spur the development of novel antibiotics. Perhaps the most important push incentive operating currently is the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X).[xxv] Second, pull incentive programs reward the success of a program after development, and consequently assures a return for the pharmaceutical company registering the new medicine, and thus an "exit" for the VC who has

funded the clinical trials. Generally, push and pull incentive programs coexist in the pharmaceutical market, in areas where stakeholders have raised concerns of limited innovation, such as orphan drugs and vaccines. Recent success with pull incentives in the development of COVID vaccines has renewed interest in the use of pull incentives to complement existing push programs to bring novel antibiotics to market. Pull incentive pilots have been recently implemented in the UK and in Sweden[xxvi], but their modest size of $10-20 million, cannot provide a sufficient reward to the risk equity investor (see *supplement*). In the US, the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act proposed a pull incentive to boost antibacterial development that would reward successful developers some $1-3 billion, on a sliding scale, depending upon conditions. In September 2023, Canada's Expert Panel on Antimicrobial Availability concluded that "*a subscription pull incentive (SPI) would work best for a country like Canada",* suggesting *"a fixed annual payment to manufacturers, regardless of sales*.", estimating the needed global reward between $2 and 4 billion dollars per antibiotics[xxvii].

Study objective

We estimate how large a pull incentive would be required to motivate private investors to commit risk capital to development of a novel antibiotic agent to address the AMR threat. Several previous studies[xxviii], [xxix], [xxx], [xxxi], [xxxii], [xxxiii], [xxxiv]have estimated the size of a pull incentive that would make antibiotics development attractive based on the construction of net present value (NPV) models (Appendix). Most analyses showed results in the $750 million - $3 billion range. This is a large range, but not unexpected, given variations in development costs, success rates and discount rate assumptions.

We add to the previous literature on this subject in three main ways. First, while the rest of the literature has used net present value (NPV) methods to estimate the size of an antibiotic market reward[xxxv], [xxxvi], we constructed an Internal Rate of Return (IRR) model because it better reflects the typical analytical approach of venture investors in this industry, and it is less sensitive to model assumptions. IRR is the *lingua franca* of the VC world and expresses a threshold annualized growth rate of return over time for investors to consider a new project. . VC fund managers think in terms of the return (%) their portfolio earns, and in many cases their own compensation depends upon IRR over a hurdle specified in their contract with Limited Partners. IRRs in the range of 10-25% are typical in the life sciences industry and an IRR of 11% approximates the average weighted cost of capital cited in the literature for corporate investors[xxxvii], [xxxviii]. Second, to populate our model, we employ newly available data from BIO Industry on probabilities of progression through the different phases of development.[xxxix] Third, we offer a simple but realistic model that is publicly available, ready-to-use and user-friendly. This enables the reader to modify key inputs and obtain flexible estimates of the reward.

Methods and Data

The goal of our modeling is to identify the size of a market reward for a novel antibiotic that would satisfy typical IRRs in the life science industry. To populate our model we used novel antibiotic clinical trial phase transition probabilities, risks and costs. We relied on the most recent published literature.

Summary of our general approach to modeling

In the Appendix, we describe how the portfolio approach to venture investing requires that successful investments make sufficiently high returns to justify investment in novel antibiotics relative to other options. The IRR expresses the expected return rate of invested capital. The investor considers four dimensions when estimating the IRR of a particular investment: Magnitude of investment capital required, Expected magnitude of exit, Time to exit, and Risk (failure vs. success probabilities).

It has been argued that capital requirements, and time to exit, are large disincentives to private sector investment in novel antibiotics. While it cannot be denied that the development of any new medicine consumes large amounts of capital and time, the authors would disagree with the conclusion that these factors account for the reluctance of private investors to enter the antibiotic market. In any given year, a vast amount of capital goes into start-up biopharmaceutical companies (around $50 billion globally in 2022, $31 billion of which was in the U.S.[xl]) and most such investment opportunities project longer time horizons and a greater capital requirement than would be expected in antibiotic development, where the clinical/regulatory path is short and simple compared to other therapeutics.

Risk can be thought of as roughly similar in antibiotics to other categories, if we consider risk as purely technical risk, defined as whether the novel compound will or will not work. There is no evidence that antibiotic drug development presents any unique or particularly difficult technical challenges compared to the discovery and development of drugs in other therapeutic categories. A good argument could be made that antibiotics carry less technical risk than other categories because the animal models in infection are quite good at predicting clinical performance in humans (as contrasted with, say, animal models in cancer). Historically, antibiotics have thus shown better progression through clinical trials, though lower progression through preclinical work.

It is expected payout - magnitude of exit - that is much worse for the venture investor in a proposed antibiotic project compared to other proposals, and hence provides the disincentive to committing funds. Working backwards, as investors do in their analyses: The commercial opportunity for a novel antibiotic is low, so the acquisition price (“exit”) can be expected to be low, so the prospective return to the venture investor upon successful exit is low. And, of course, that successful exit may not happen. The net result is a “pass” by the investor. Our methodology quantifies the magnitude of exit needed to provide a financial incentive for the investor.

Summary of empirical approach

Figure 1 summarizes our empirical approach. We created a bottom-up model based on the costs of each stage of drug development, the duration, and the probability that a drug candidate would succeed at progressing from one stage to another, in order to arrive at a risk-adjusted cost per stage.

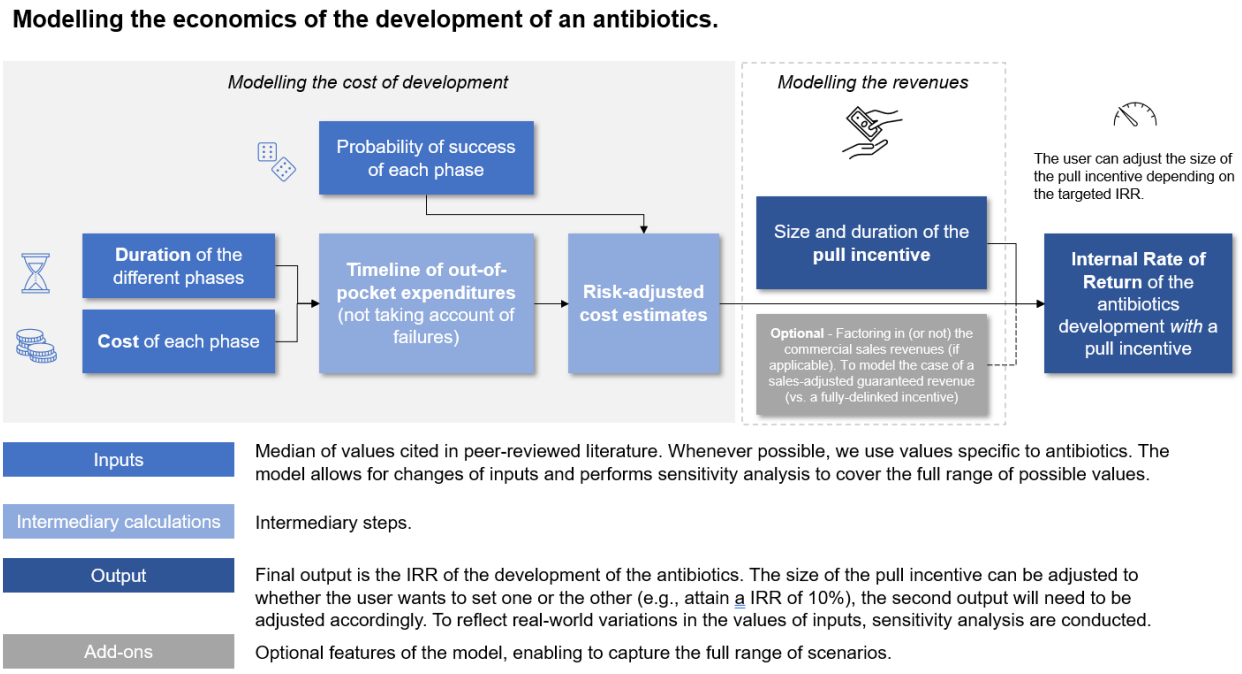


Figure 1: Modelling the economics of the development of an antibiotic.

We combined inputs from all relevant sources on each of the measures (costs, duration and probability of progression) based on a review of the previously published literature on this topic (see Appendix) and generally used the median value on each measure. Importantly, where possible we used inputs that were specific to antibiotics rather than to drug development in general.

We then assumed that a reward would take place upon approval by the FDA or the EMEA, and be paid over a period of ten years, as others have modeled[xli], [xlii].

Finally, we measured expected IRR, at different reward levels, and their sensitivity to various assumptions.

The "answer" of how large a pull incentive is required must, of necessity, be expressed approximately or as a range. This is reflective not of imprecision in measurement or analysis but of a range of different situations in the drug development universe. Therefore, we use our model to produce a range of estimates, based on different assumptions and measure estimates drawn from the literature. The model is available as an excel file in the Supplement and is interactive to

allow inputs to be modified by the user. The model permits the reader to conduct her own sensitivity analysis to the assumptions.

Detailed description of the estimation

The IRR model is built with three major phases:

First, we model the economics of the antibiotic's development.

Inputs: the model uses three main inputs: the three key features of the development of the antibiotic candidate (cost, duration, and probability of success of each phase). The values used in the model are based on data from peer-reviewed literature relating to phase duration, phase probability of success and drug development costs. Data points used in the model are medians of the data collected, to avoid biases created by outliers (when possible, we used data specific to antibiotics). A complete list of the sources used is available on the published model, under the "Sources" tab.

Computations of risk adjustments: the costs are risk-adjusted to account for the failure of programs (drugs that do not progress to the next phase of trials). To do so, we assumed that the modelled research and development efforts would result in the creation of one antibiotic approved by the regulatory agency at the end of its development. Then, the number of candidate drugs needed at the outset of each phase was computed, based on the probabilities of success of each phase (if 1 approved drug must be produced, and if the probability of success of approval is 80%, then 1/0.8 = 1.25 drugs are needed at the end of Phase III). Costs are thus risk-adjusted by multiplying the cost of each phase by the number of drugs needed at this phase to eventually produce one approved drug. We began with a "hit" identified – a compound that has activity against the target, and progressed to conclusion. We thus do not include the costs of the earliest stages of discovery, such as screening compounds for hits, or genetic modeling.

Output: the Internal Rate of Return (IRR) of the antibiotic development project is computed. IRR measures the annualized return on capital, and is independent of investment size and discount rate. These metrics enable the user to evaluate the financial attractivity of the development of an antibiotic (with or without the Market Entry Reward).

Second, we describe and model the effect of a pull incentive on the IRR of the antibiotic's development.

In this model, the pull incentive is a market entry reward (MER). The reward is a succession of payments to the sponsor of the antibiotics, paid after the antibiotic is approved by the regulator. The pull incentive is described through three main features that can be adjusted:

> First, the beginning date -when the pull incentive begins to be paid in the drug development process
>
> Second, the duration – whether it is a lump sum payment, or regular payments, spread over a given number of years; and
>
> Third, the magnitude – the total of the payment amounts.

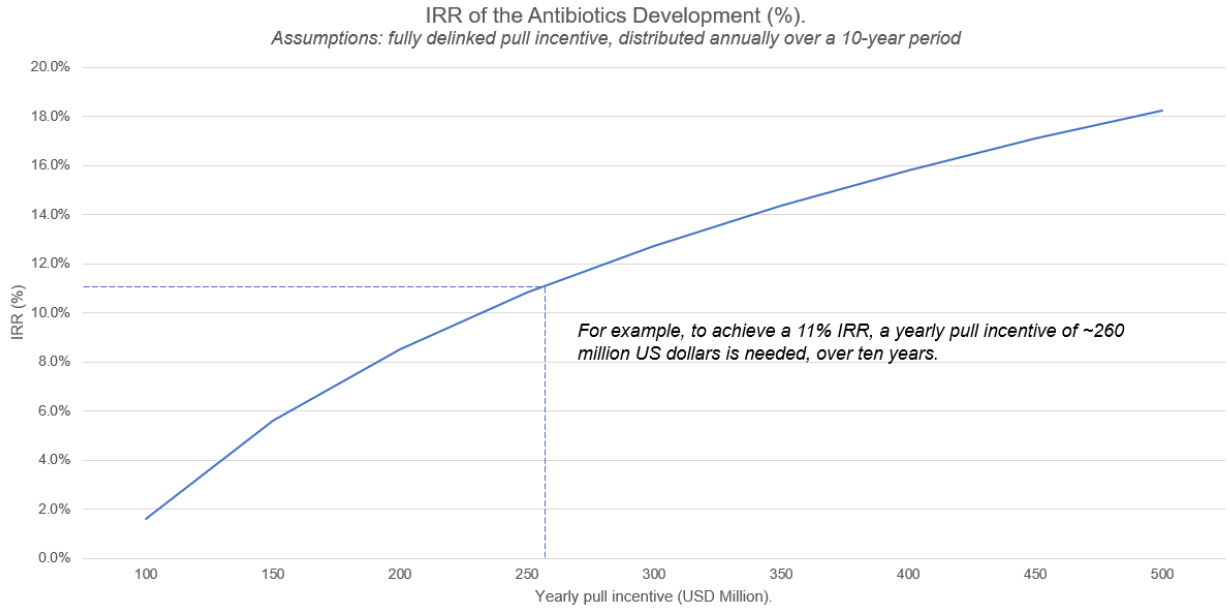
Third, we model sales of the new antibiotic after approval.

A simple model of the revenues generated by commercial sales has been added to the model. It enables the user to study the effect of sales on the needed pull incentive. Different approaches are possible. For example, in a "volume-independent" (sometimes called a 'fully delinked' model) reward, sales can be set to zero since the reward is not dependent on sales volume after launch[xliii], [xliv]. By contrast, in a "sales-adjusted" reward, the expected sales can be taken into account, to see how the reward could be tailored to the expected sales revenues of the antibiotic. In our base case, we assumed peak sales of $50 million annually, achieved two years after launch, and we assumed that the reward could be reduced to account for those commercial sales. This can be adjusted. A case can be made for higher peak year sales: a 2021 study estimated that peak year sales of a new antibiotic might be $127-184 million.[xlv] At the other end of the range of assumptions, a WHO report proposed that some novel antibiotics not be used at all – essentially demanding zero peak year sales.[xlvi]

Results

Our results show the increase of IRR with reward size (Figure 2).

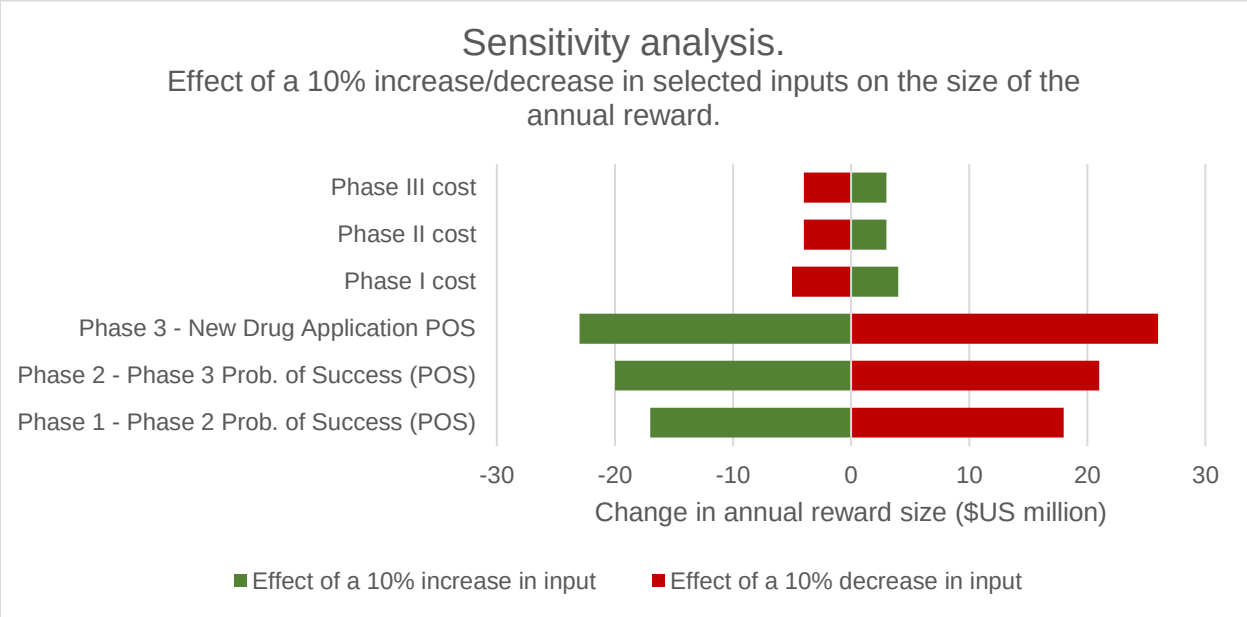
Figure 2: IRR as a function of the yearly pull reward size.



For example, to achieve an 11% IRR, a yearly pull incentive of $260 million (in 2023 dollars) during the ten years following approval, amounting to a total reward of approximately $2.6 billion, would be required. To achieve a 6% IRR, a yearly incentive of $150 million would be needed, and to achieve an IRR of 18%, a yearly incentive of $500 million would be needed.

Figure 3 (below) shows the sensitivity of the pull reward size to other IRR model inputs. The probability of advancement to the next phase is considerably more important than the cost of the phase, reflecting the large risks in drug development.

Figure 3: Sensitivity of Pull Reward Size to Other IRR Model Inputs.



In our baseline scenario, we have not added overhead to our cost estimates, noting that published costs generally do include most components of overhead. Our model does give the flexibility to include additional overhead costs, following Outterson (2021) who suggested that additional overhead needs to be added to published cost estimates thus raising the estimated costs of development and the magnitude of the pull incentive.[xlvii]

Discussion

Our results suggest the size of a market reward for novel antibiotics is sensitive to IRRs and that to achieve an IRR of 11%, a yearly pull incentive of $260 million (in 2023 dollars) during the ten years following approval, would amount to a total reward of approximately $2.6 billion.

An IRR of 11% is our preferred target because it measurably exceeds the 10.5% weighted average cost of capital in the pharmaceutical industry as reported by Baras[xlviii], and is close to the 11.5% long-term performance benchmark of venture capital as measured by Reiner[xlix].

Arguments could be made in favor of a higher IRR target. A drug selling $260 million a year would not be a high-volume "win" and surveys have suggested that venture capitalists seek returns in the 20% range.[l,li] These higher returns may be necessary if the developers are pursuing not an extension of a known class of antibiotic but a truly innovative, higher-risk first-in-class therapeutic.

The counter-arguments for a lower IRR target are that perceived risk is lower with the guarantee of a reward for success, otherwise uncertain, and that a large social benefit is delivered. Further, some recent industry estimates suggest realized IRRs in the life sciences industry have been more in the range of 4-6% IRR, suggesting our estimates may be larger than current market conditions may require for private VCs to fund[lii]. Also, our 11% IRR target may also be an overestimate of the return needed for governmental investment or public-private partnerships. In this setting it is possible that the IRR is thus endogenous to other pull incentive details. One advantage of our approach over typical NPV models is that our model is flexible and can accommodate a range of assumptions of % IRR.

We believe that an 11% IRR should be sufficient to provide incentive to the private sector to invest in novel antibiotic development as it exceeds the average weighted cost of capital cited in the literature for corporate investors[liii], [liv].

With an 11% IRR target, results of our model suggest a pull incentive to bring one new antibiotic to market is in the range of $2.0 - 3.5 billion. These results do not differ a great deal from estimates by others in previously published studies using different methods (see Appendix), that are largely in the $1-3 billion range and is very close to the 2021 estimate by Outterson of $3.1 billion[lv].

One antibiotic drug alone, of course, would not be sufficient to meet society's needs for new agents against the growing AMR threat. Previous work[lvi] has suggested that six new drugs would

be called for, over a ten-year period. Thus, using the 11% IRR result, the total public expenditure on this proposed pull program might be 6 x $2.6B = $16B, if each of the six new agents is rewarded independently. As each "reward" is paid over a ten-year period, and the rewards are earned at different times during a ten-year interval, the payout would take place over 10-20 years.

One way to think about our estimates of a pull incentive for AMR (6 x $2.6 B = $16B, spent over 10-20 years) is to compare it to the cost of maintaining the *status quo*. In 2023, OECD studied the cost of AMR to 34 OECD countries (the United States, the United Kingdom, all 29 EU/EEA countries, Japan, Switzerland, and Türkiye[lvii]). It estimated that if observed resistance trends continue to follow the expected growth rates, AMR could cost $28.9 billion per year up to 2050 for the health systems of those 34 countries to "treat complications caused by resistant infections". AMR could also cause a total economic loss of $36.9 billion per year across the 34 countries, caused by reduced workforce participation and productivity. Thus, in contrast, the estimated total pull incentive of $16B (total, paid over 10-20 years, or $0.8-1.6B annually to obtain a 11% IRR) pales in comparison to an annual direct cost of $29B and the annual indirect economic cost of $36.9B.

These estimates are large, but not excessively so, and appear affordable by the U.S., the world's largest national economy, acting alone, or several national economies acting in concert. For perspective, the annual budget of the National Institutes for Health is $48 billion[lviii] and the annual budget of the FDA is $6.2 billion, of which $2.9 billion is accounted for by user fees.[lix]In contrast, we note that the UK's pull incentive program is currently GBP 10M per annum (roughly $13M) and will rise to only GBP 20M per annum[lx] Our estimates suggest this national pull program alone, in a smaller economy, is insufficient to provide financial incentive to a drug developer for one new antibiotic, as would be expected. However, it is not far from the $19M that is estimated by Outterson as the "fair share" for the UK in a collaborative G& & EU27 program.

Structuring a pull incentive for novel antibiotics raises additional questions, including how the reward should be structured, how the reward should be paid, how many parties would be eligible to receive a payment, would commercial sales into the healthcare system (if any) reduce the required payment by the sponsoring entity or would it be a "bonus" and who should guarantee the reward. Other authors have discussed these design and other questions at length[lxi] and therefore here we provide some limited comments on these topics informed by our efforts.

First, the reward could be structured as a one-time lump sum payment, or could be spread out over several years. From our perspective, the sponsoring entity might prefer a payment spread over five or ten years, both because it reduces the present value of the reward and because it eases cash flow demands, which is important for governments operating on an annualized budget. The company on the receiving end might be expected to prefer a one-time lump sum payment because it is more financially valuable (i.e., has greater present value) than the same amount spread over a 5–10-year period. For perspective, the 11% IRR achieved with an annual reward of ~$260 million for ten years ($2.6 B total) is roughly equivalent to that of a single $1.8 B payment at market launch. On the other hand, a guaranteed cash flow over a decade may be

attractive to a small startup company if it can use the investment to attract additional capital, or to a more established publicly-traded company which may view this payment as an annuity. The consensus today (and the structure by which models are compared) is a ten-year payout.

Second, guaranteeing the reward is important. Time inconsistent preferences from sponsors is known to reduce investment in innovation. In the absence of guarantees, an investor might fear that the reward is withdrawn after the investment is made. We refer the reader to the history of the U.S. Superconducting Supercollider, for which funds were allocated by the U.S. Congress and then retracted, leaving an enormous hole in the Texas desert. In this case, the U.S. government's ambition to build a high-energy accelerator to support research was undermined by the withdrawal of international partners (Europe, Japan, Canada), which were originally supposed to share the costs but never delivered in the end.[lxii] Consequently, we recommend protecting long-term investments in new antibiotic development from the future preferences of sponsoring agencies who might wish to undo it.

Third, some of the "reward" can be paid early, at risk. This could involve paying a portion of the reward upon successful completion of a Phase II trial, a so-called "milestone prize model." This reduces risk and expenditure for the investor, and the government absorbs some of the risk of Phase III failure.

The economics will differ for a later-stage drug. In our model, the estimated pull incentive amount required is calculated for a drug currently at the outset of the pre-clinical phase. The magnitude of the incentive needed will vary with the maturity of the starting point, and could be considerably lower for a more mature asset, with some portion of the development risk (and cost) retired.

Some initiatives have proposed excluding drugs already in late stages of development. Instead of excluding such drugs, we might propose that the model be leveraged to recalculate the necessary reward for later-stage drugs, which would, of course, be smaller, as some of the risk-adjusted expenditure has already occurred.

Fourth, we believe it is not preferable to limit the reward to one "winner" as such a model may not provide sufficient incentive to the investor, who must be concerned that her expensive and risky effort can succeed clinically only to finish second. Rather we suggest that numerous parties should be eligible to receive a payment, similar to how the COVID vaccine and pneumococcal advanced market commitments were structured. The reward amount can be split or can be duplicated for subsequent developers. If duplicated, costs multiply. If split, financial incentives are reduced for each developer, and may not prove sufficient.

Fifth, the government may actually take delivery of product and stockpile it, or it may choose to provide a cash payout for success, and not take delivery or some combination of the two. This can be thought of as a "call option" on the new medicine, where the government has the option to purchase a volume of the medicine at a low price, and pays highly for the option[lxiii]. This can be thought of as keeping the capacity online, to use as (and if) needed.

Sixth, commercial sales into the healthcare system (if any) might reduce the required payment by the government, or could be considered a "bonus" to the developer. Proponents of pull incentives have advocated for both sides of this argument. Allowing the developers to sell outside the government contract can increase their financial incentive, but it also provides incentives for the developer to promote the use of their products, thus harming the fight against the development of resistance. Another factor for the government is that commercial sales can be used to reduce the reward amount, thus providing a guarantee with a floor for the developer, but with the opportunity of reducing the cost to the government. Perhaps the best option to promote global access to new antibiotics is to restrict sales of the drug in-country to the sponsoring government, but permit foreign sales to other geographies, thus not depriving others of a valuable medicine.

Finally, we do not see why this needs to be a single-government initiative, but rather it may be fiscally prudent to make it a multinational effort. We note that a public antibiotic initiative (whether push or pull) can suffer from "free riders" who benefit from the development of a new drug without paying for the costs of development. This problem, and the large capital costs involved, might make this project politically untenable to all (but the largest - U.S.?) economy, and it would be impractical to expect a global funding effort. But a G7 effort may be possible, and some early discussions have opened the topic. Allocation of expenditure may be expected to be apportioned according to the GDP of the participants. Some collaborative effort will be indicated to define target pathogens and measures of success. However, it is possible that contributing collaborators do not entirely agree, and that target and quality metrics differ somewhat. This creates some risk that a development effort qualifies for some of the multinational reward, but not all.

We note with approval that some governments are devoting attention to the issue. In June 2021, Senator Michael Bennet, Senator Todd Young, Representative Mike Doyle and Representative Drew Ferguson co-sponsored a bill aimed at addressing the market failure undermining the development of novel antibiotics: **the PASTEUR Act** (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act[lxiv]). This act is intended to "*establish a subscription-style model which would offer antibiotic developers an upfront payment in exchange for access to their antibiotics, encouraging innovation and ensuring our health care system is prepared to treat resistant infections*."[lxv] In practical terms, the federal government would sign an agreement with antibiotics developers, which would be paid contractually agreed subscription payments over 5+ years, in the exchange for the development and supply of critically needed antibiotics. The monetary values of the contract cited in the bill ("between $750 million and $3 billion, depending on the characteristics of the developed antibiotics") are consistent with the range of values computed by our financial model. Please see the Appendix for further detail of elements of the PASTEUR Act.

In addition to the study limitations we have already discussed, we caution that our results can only be a rough estimate for the general case. Each actual drug development project will have its own costs and probabilities, and the outputs are fairly sensitive to the assumptions of costs, timing and probability of success, as shown earlier.

In summary, we assert that the establishment of pull incentives will be critical to the development of new antibiotics. Some currently discussed policy options such at the PASTEUR Act in the U.S. would establish such a program. Our work supports this approach, and our results suggest that the reward amount would vary with investor expectations of a return on their investment. With an IRR of 11%, low for private VC investment, but within range, a market reward would amount to $2.6 billion per new antibiotic successfully developed. The cost of six new antibiotic agents developed over the course of a decade would amount to $16 billion.

The cost of a pull incentive program that engages the private sector to develop novel antibiotic solutions is modest, compared to the huge social costs that can be expected to be incurred as a result of the continued expansion of antibiotic resistance. This cost need not be borne by a single national government, it can be shared among several national governments and/or private philanthropies dedicated to public health. However, given the long lead times required in drug development, it would be wise not to wait, but to begin such a program immediately, to address the current public health crisis and avoid an even larger one in the future.

Appendix

An illustration of the IRR model

Based on our experience and interviews with practitioners in the field, we observe that investors are looking to optimize return on an entire portfolio of high-risk investments. In shorthand, the investor may describe a return on a specific investment as a "multiple" of capital deployed ("2x" or "4x", e.g.), but the astute investor appreciates the time value of an investment and will include that consideration in calculating an internal rate of return on his capital. For example, a "2x" return in one year is equivalent to an IRR of 100%. The same 2x return in two years is an IRR of 41%, in three years 26%, and in four years just 19%. Higher risk investments are expected to offer a higher return, and the data available demonstrate that, indeed, the earliest, highest-risk investments do return greater payoffs on average, but with concomitant greater volatility and greater risk of losing the entire investment. In the VC world, a prospective investment portfolio (or "fund") is expected to project an IRR on the order of 20-25% (depending on risk). If the capital is tied up for five years, that implies a multiple upon exit of at least 2.5x for the portfolio. For each investment in the portfolio that fails, the returns on the successes must be greater. We offer the following illustrative model portfolio.

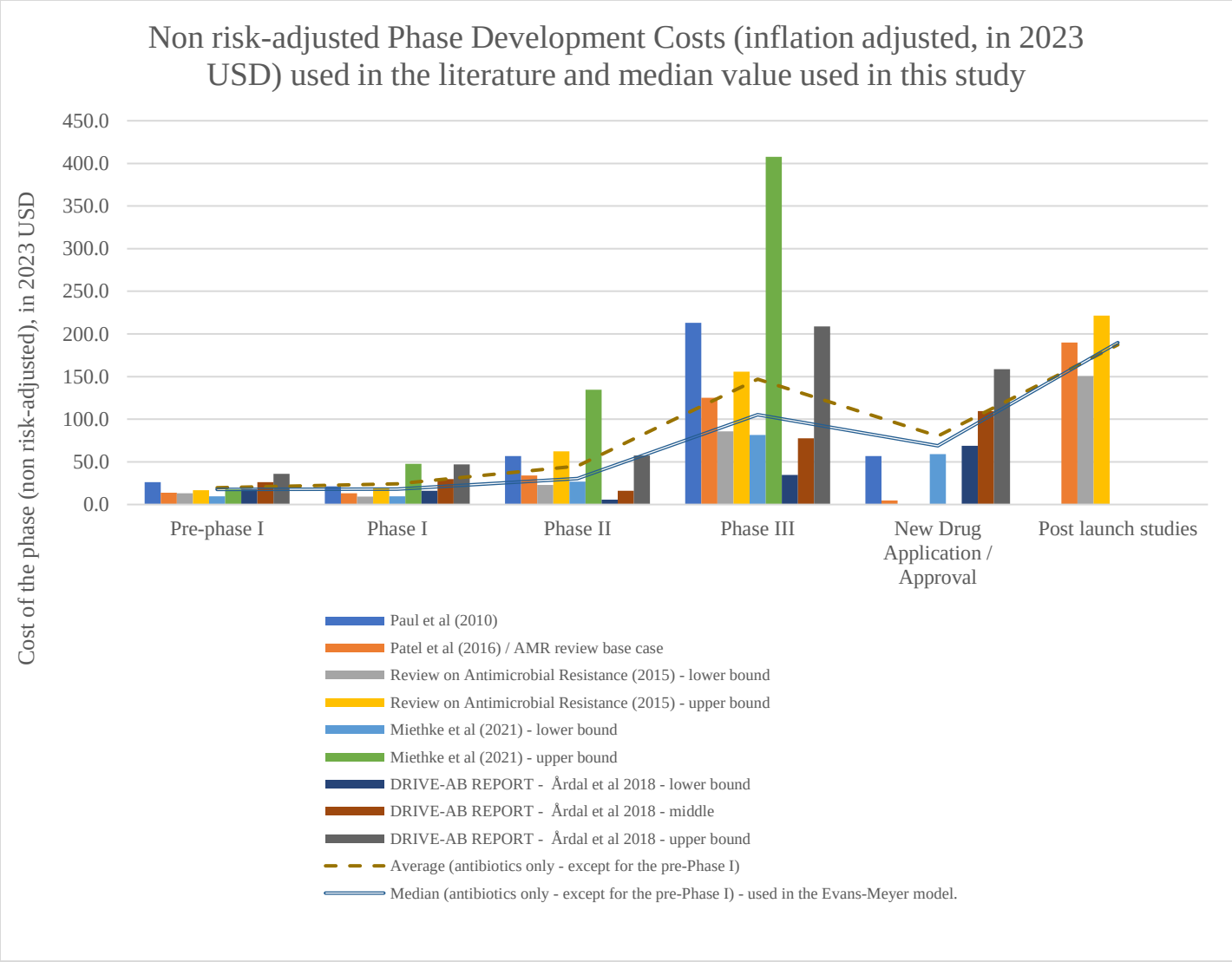
Table 2. Illustrative Model $100M Portfolio

Investment	Invested	Return	Time to Exit
A	$20M	bust	n/a
B	$20M	bust	n/a
C	$20M	bust	n/a
D	$20M	$20M	five years
E	$20M	$220M	five years
TOTAL	$100M	$240M	five years

The investor, of course, is hoping that *all* the investments succeed and produce a large exit, but the realistic expectation is often similar to the above: 60% fail, 20% return the original capital and 20% provide a large success that accounts for the positive return on the entire portfolio. Note that in the above example, the entire portfolio returns $240M on a $100M investment over five years, or roughly a 19% IRR. The winning investment, however (Investment E) has provided an IRR of nearly 62% on an 11x return of capital.

The investors are very focused on the exit, which is the only way they earn the return they are looking for, and their time horizon will be several years, but not forever (and depends, of course, on the investor). The general partner, making the investment decisions, will seek investment capital from the limited partners for a "fund" that may have a planned life of five to ten years. Investments will be made over the first two years of the fund and harvested over the latter years. The average time from initial investment to exit (in 2019) was 6.3 years.[lxvi]

If we consider an investment in a novel antibiotic drug development, we must recognize that the exit may be well beyond five or six years, and hence the return (in the model portfolio above) must be greater than 11x. If the development effort has consumed $50 million (a reasonable number – see later in this paper for a detailed analysis of development costs) then an exit need be on the order of $600 million – unrealistic for an acquisition by a large pharmaceutical firm, and far above the usual market valuation for an independent antibiotic company.



Appendix Figure 1. Phase development costs, in the published literature, and as used in this model.

Source	Key findings	Key Assumptions
Sharma and Towse (2011)[lxvii].	"The purpose of the model was to determine the size and timing of the different incentives needed in Europe to increase the NPV of antibacterial R&D to $200 million" The authors suggested the idea of an Advance Market Commitment (AMC) (that is, "a commitment by a government or a private/international organization to purchase a specified quantity of a drug or a vaccine that meets certain criteria pre-specified by the purchasers at a pre-determined price"). The authors estimate that a 5-year AMC of **1.4 billion** (275 million per year) would increase the NPV of the antibiotics development from -38.15 million to +150 million.	• Based on Paul et al (2010) and DiMasi et al (2010) assumptions • Discount rate: 11% • Peak year sales: $419 million • Preclinical: 5.5 years, 13.63 (millions €), POS: 35% • Phase I: 1.5 years, 11.06 (millions €), POS: 58.2% • Phase II: 2.5 years, 29.48 (millions €), POS: 52.2% • Phase III: 2.5 years, 110.55 (millions €), POS: 78.6% • Approval: 1.5 years, 29.48 (millions €), POS: 91%
Sertkaya et al (2014)[lxviii].	The objective of the authors was to estimate the "*the level of each incentive (in dollars) that would equate the private ENPV to $100 million*[1] *for a drug sponsor that is at the start of pre-clinical phase*". *"For example, in order to achieve the $100 million threshold for ABSSSI [a given antibiotics - Acute bacterial skin and skin structure infections] sequential payments (in millions of dollars) of $59, $76, $165, $495, and $124 would be required at each successfully completed phase of development listed in the table for* ***a total payout of $919 million dollars over time****."*	*Phase: duration, cost, probability of success (POS)* • Pre-clinical: 5.5 years, $21 million, POS: 31% • Phase 1: 1.5 years, $30 million, POS: 54% • Phase 2: 2.1 years, $45 million, POS: 60% • Phase 3: 2.5 years, $210 million, POS: 67%. • New Drug Application (NDA): 0.8 year, $2 million (fee), POS: 85% • Cost of capital: 11% • Sales: *"$793 million per year for 20 years (i.e., approximately $1.5 billion total)."*
Review on Antimicrobial Resistance (2014). (AMR Review)[lxix]	Among the authors's suggestions is the idea of a "*giving a lump sum payment to companies who come up with new antibiotics, according to their value to society, but also allowing them freedom to sell their drugs for a profit*." "*We estimate that* ***a lump sum of between 1 and 1.3 billion USD*** *to cover development costs of a new drug on average, including costs of projects which fail along the way. The advantages of this system are that it offers drug companies protection against the risk of investing in this area, whilst also rewarding those who come up with more useful drugs.*"	• Cost of capital: 11% In the base case: • Preclinical: 5.5 years, $10 million, POS: 17.3% • Phase 1: 0.9 year, $10 million, POS: 33% • Phase 2: 1.1 year, $26 million, POS: 59.3% • Phase 3: 1.8 years, $96 million, POS: 75.8% • Approval: 0.75 year, $4 million, POS: 79.7% • Post-approval: 3 years, $146 million
A Call for Concerted Action on Antibiotics Research and Development Global Union for Antibiotics Research and Development report, commissioned by the	"*To achieve an expected net present value of ~$300 million* ***a Global Launch Reward of $1 billion per launched antibiotic*** *is required. This estimate is comparatively low relative to other estimates, which range from $1 billion to $4 billion*."	Assumptions on phase probabilities and lengths are similar to that of the AMR Review. • Total development costs: $600 million • Discount rate: 9% • $300 million peak sales

[1] The authors note that : « *While the selection of a $100 million threshold value is somewhat arbitrary, the figure is comparable to the figures used in other similar analysis and has been indicated as being the tipping point for smaller companies by some of the experts interviewed for the study*."

German Federal Ministry of Health (2017)[lxx]	The authors note: "*The small and medium-sized biopharmaceutical companies interviewed for this report have estimated an expected net present value of $200–300 million to be highly attractive.*"	• Volume-independent payment over 8 years: "*Of the total value of $1 billion, $600 million will be paid out in the first three years. The remaining $400 million will be paid out over years four to eight of commercialization*".
Årdal et al (2018)[lxxi].	*"DRIVE- AB has determined that **a market entry reward of $1 billion per antibiotic globally (in addition to unit sales revenues)** could quadruple the number of new antibiotics coming to the market in the next 30 years.*	Triangulation of data on antibiotic development times, costs and probabilities, based on Sertkaya et al. (2014).
Towse A, et al. (2017)[lxxii]	*"We evaluated the impact of […] an 'insurance model' based on a global flat annual fee, apportioned to, and paid by, each healthcare system, coupled with a price paid by healthcare providers to the manufacturer for each unit of drug used".* *"Under the insurance model, with no additional incentives and with a fixed price per day of $120 ($1680 per 14 day treatment course), the fee for global markets combined would be **$262 million per annum for ten years (a total of $2.6 billion)** to attain an eNPV of $100m."*	Preclinical: 5 years, $19m, 35% Phase 1: 1.3 years, $16m, 35% Phase 2:2.2 years, $54m, 35% Phase 3: 2.4 years, $196m, 35% Registration/Approval: 0.9 year, $29m, 35%
WHO (2020)[lxxiii].	The model developed by the authors enables to model the development of a portfolio of antibiotics.	Literature review, company filings and feedback/data received from industry experts. Discovery and preclinical: 3.8 years, $14.7 million, 36.7% Phase I; 1.5 years, $10.1 million, 61.0% Phase II: 1.9 years, $26.3 million, 45.6% Phase III: 2.0 years, $96.3 million, 69.1% Registration: 1.1 year, $15.5 million, 87.5% Post-launch: early commercialization, $ 46.9 million Post-launch: studies, $48.5 million
Outterson (2021)[lxxiv]	The author recommends the use of pull incentives, in addition to current push incentives. The size of pull incentives is estimated as "**several billion dollars** [to be added to] the global revenue stream of a highly innovative antibacterial, reduced by any grants received supporting clinical development of that product."	Literature review.
Boston Consulting Group (2022)[lxxv]	"Our cost-based approach yields a minimum incentive per first-to-market (in its class) antibiotic between $2 billion and $3 billion, paid out over five to ten years."	Not disclosed: "Our own analysis uses data collected from other antibiotics-specific models and refined with industry experts."

Figure. PASTEUR act elements

Characteristics	Description
Nature	Contract between the federal government and the antibiotics developer
Key principle	Encourage the development of needed antibiotics by giving antibiotic developers an upfront payment in exchange for access to their antibiotics
Eligibility criteria	To be eligible, the antibiotics needs to: - be FDA-approved - meet unmet AMR needs (as identified by the experts of the "Committee on Critical Need Antimicrobials", in charge of the identification of critically needed antibiotics).
Typical timeline	**Step 1: Application** During clinical development, the antibiotics sponsor applies to have an antibiotic designated as a 'critical need antimicrobial' and transmits clinical and preclinical data. **Step 2: Designation** The transmitted data is evaluated. If the antibiotics is deemed likely to meet identified unmet needs, a monetary value is calculated for contract the drug developer would be eligible to receive.
Terms & Conditions	The developer must: - *"Ensure commercial and federal availability of the drug* - *Identify, track, and publicly report available drug resistance data and trends related to their critical need antimicrobial* - *Develop education and communications strategies for health care professionals and patients about appropriate use of their drug;* - *Submit a plan for registering their drug in other countries where an unmet need exists;* - *Ensure a reliable drug supply chain, thus leading to an interruption of the supply of the drug in the United States for more than 60 days;* - *Make meaningful progress toward completion of FDA-required post-marketing studies* - *Produce their drug at a volume negotiated* - *Price their drug no lower than a comparable generic drug* - *Abside by manufacturing and environmental best practices"*
Payment nature	Subscription payment Fully delinked: decoupled from the volume of antimicrobials sold and used.
Estimated payment value	The monetary value of the contract shall vary between $750 million and $3 billion, depending on the characteristics of the developed antibiotics.
Payment characteristics	*"Contracts under this subsection must run for a period of at least 5 years. The section authorizes 3 possible maximum periods; these are: the greater of (a) 10 years, (b) the*

	remaining time on the 5 sponsor's patent protections, or (c) the remaining exclusivity period with respect to the antimicrobial drug. *Payments will be made in equal annual installments with an option for companies to redeem part of the last year contract value in the first year of the contract in order to offset costs of establishing manufacturing capacity.* *The subscription contracts will remain in place even if a microbe that is treated by the drug is later removed from the Committee's list of infections."*

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