Incenting the Development of Antimicrobial Medicines to Address the Problem of Drug-Resistant Infections

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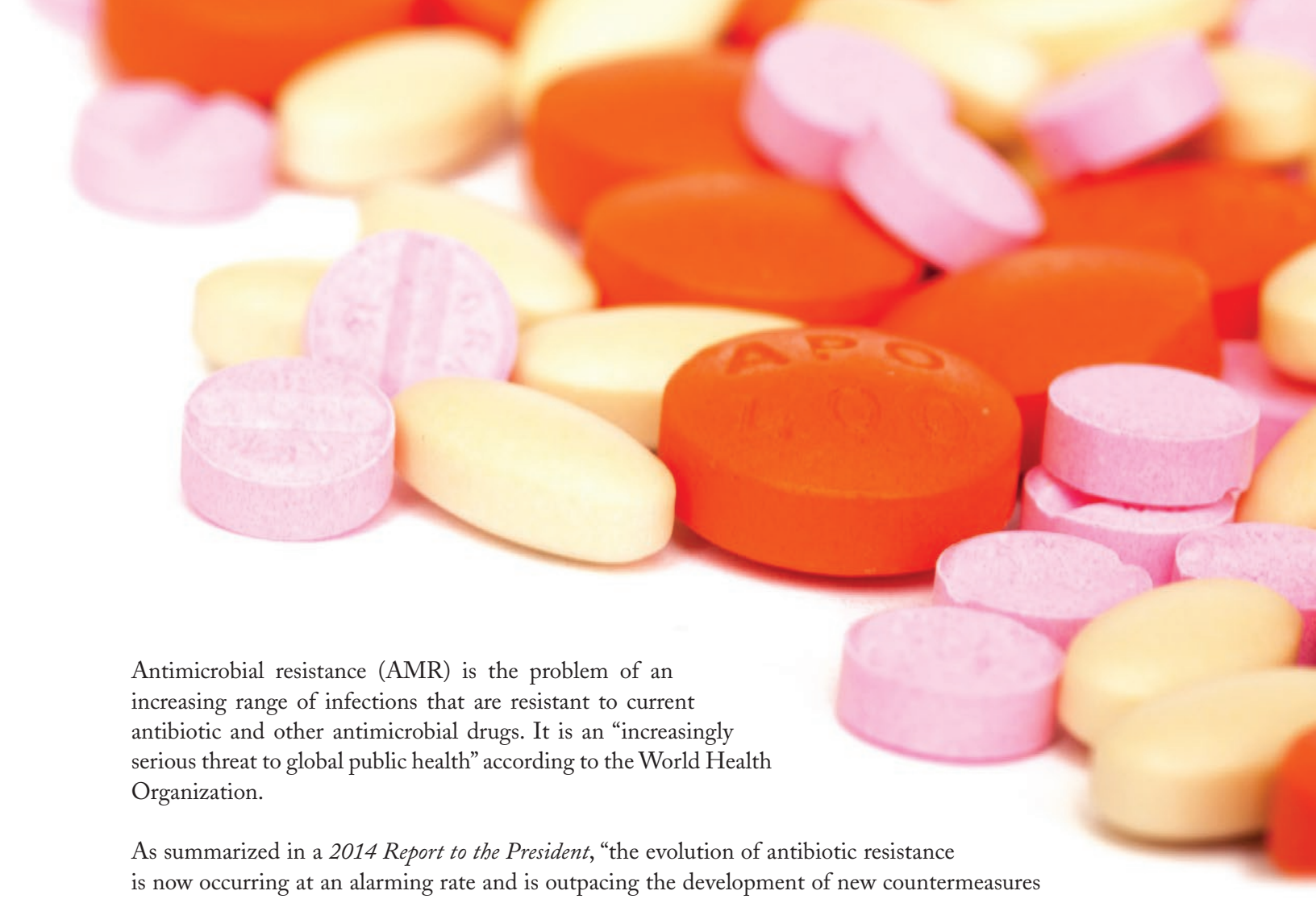


Antimicrobial resistance (AMR) is the problem of an increasing range of infections that are resistant to current antibiotic and other antimicrobial drugs. It is an "increasingly serious threat to global public health" according to the World Health Organization.

As summarized in a *2014 Report to the President*, "the evolution of antibiotic resistance is now occurring at an alarming rate and is outpacing the development of new countermeasures capable of thwarting infections in humans. This situation threatens patient care, economic growth, public health, agriculture, economic security, and national security."

The International Federation of Pharmaceutical Manufacturers summarizes the problem stating that:

> There is a dearth of new antibiotic medicines as the growth in antimicrobial resistance has been accompanied by a sharp decline in the development of new antibiotic medicines. Over the past three decades only two new classes of antibiotic medicines have been discovered, compared to 11 in the previous 50 years. It is now widely accepted that the increase in resistance and the decline in the number of new drugs coming to market together pose a major threat to health in all countries. The number of antibiotics becoming obsolete due to resistance significantly exceeds the number of new therapies being approved. Concerted action is needed to boost antibiotic development, to face a growing public health threat.

More and more microorganisms will continue to gain resistance to the current drug therapies because AMR is basic evolution. These evolutionary changes will occur regardless of the number of new antibiotics approved. Consequently, an adequate pipeline of new therapies to cure these infections is always necessary. Without such a pipeline, the health risks associated with current diseases grow.

The threats include diseases from bacteria, as well as diseases associated with fungi, viruses, and parasites. If not effectively addressed, the health implications from the growing AMR problem are severe. Our ability to treat parasitic infections, such as malaria, or viral infections, such as the flu and HIV, will decline. The success rate

from modern medical treatments, such as chemotherapy and organ transplantation, could also suffer. And, the problems are not theoretical. According to the Centers for Disease Control and Prevention, "each year, at least 2 million people become infected with bacteria that are resistant to antibiotics, and at least 23,000 of them die."

Beyond the human cost, "the Centers for Disease Control and Prevention (CDC) estimates that the annual impact of antibiotic-resistant infections on the U.S. economy is $20 to $35 billion in excess direct health care costs, with additional costs to society for lost productivity as high as $35 billion per year and 8 million additional days in hospitals. And the problem is worsening."

A September 2016 World Bank report noted that

> In the optimistic case with low AMR impacts (modelled as shocks to the labor supply and to livestock productivity), global GDP fell short by 1.1 percent annually by 2050; the shortfall exceeded $1 trillion annually after 2030. In the high AMR impact scenario, global GDP fell short by 3.8 percent annually by 2050, and the shortfall reached $3.4 trillion annually by 2030. In both scenarios, the absolute amounts of annual losses would double by 2050.

Addressing this burgeoning health crisis is an important medical need, and in response, the Prime Minister of the U.K. commissioned a *Review on Antimicrobial Resistance* (often referred to as the *O'Neill Report*). The *Review* proposes a series of 10 very broad steps that include public education campaigns, increased incentives for developing medicines that address the AMR problem, and increased public funding for early-stage AMR research. In total, their estimate "for the cost of taking global action on AMR is up to 40 billion USD over a 10-year period."

Similarly, the *2014 Report to the President* noted three broad areas that require action: improving surveillance of antibiotic-resistant bacteria; increasing the longevity of current antibiotics by improving appropriate use; and increasing the rate at which new antibiotics, as well as other interventions, are discovered and developed.

The purpose of this study is to review the strengths and weaknesses of the proposed development incentives for antibiotics and antimicrobials.

Implementing many of the proposed steps are straightforward and relatively non-controversial. For instance, hand washing is a highly effective/low-cost way to reduce the spread of infections. By reducing the number of infections and, therefore, the need to prescribe antibiotics and other antimicrobials, fewer bacteria, viruses, and fungi will be able to develop resistance to the available medicines. Education campaigns that emphasize the benefits from hand washing are, consequently, important public health programs.

Another straightforward policy would address the problem of antibiotic overuse and over-prescription for both people and animals. These overuses of antibiotics do not improve human health, and have been linked to adverse health outcomes. Therefore, curbing the overuse of antibiotics can increase overall human health while helping to address the AMR problem.

As documented by Bruce Gellin, the Director of the National Vaccine Program Office for the Department of Health and Human Services, greater use of vaccines also has an important role to play.

Vaccines prevent bacterial infections, and by reducing the number of infections, reduce the number of opportunities for microorganisms to develop resistance to the available medicines. Wider use of current vaccines, and the development of vaccines that target microorganisms that are resistant to current therapies, are therefore important strategies for addressing the AMR problem.

Other policies are more complex, in particular, incenting the development of more antimicrobial medicines (new antibiotics and vaccines) that will be effective against AMR microorganisms. Policies that successfully spur the development of these medicines must be based on a thorough understanding of the disincentives that are currently inhibiting their development. These disincentives are well-recognized: despite the medical need, and despite the generally strong return on investment for many other drug classes, the return on investment for developing new antimicrobial medicines (particularly antibiotics) is too low.

The purpose of this study is to review the strengths and weaknesses of the proposed development incentives for antibiotics and antimicrobials. The best policies will counter the disincentives that are currently discouraging the development of antibiotics and antimicrobials and create positive incentives that resemble the potential returns in other drug classes. Toward this end, the success of the Orphan Drug Act is an important case study. Leveraging these lessons, policies that reduce regulatory costs and offer transferable and expanded exclusivity hold great promise. When coupled with effective investments in basic research, this approach can substantially improve the incentives for innovators to develop new vaccines, antibiotics, and antimicrobials and effectively reduce the global health threat from AMR.

BENCHMARKING TO A FREE MARKET PRICE SYSTEM

In most markets, implementing policies to alter the incentives of producers or consumers are unnecessary. Prices will typically provide the necessary information on scarcity and want. Prices will also simultaneously serve as a positive incentive, or an encouragement to engage in an activity, and a negative incentive, a discouragement from engaging in an activity.

For producers, rising prices are a positive incentive that encourage entrepreneurs and producers to provide more current goods and services, find better ways to produce current goods and services, or create new goods and services. For consumers, rising prices are a negative incentive that discourages consumption. The reverse is true for falling prices. Falling prices are a negative incentive for producers, discouraging greater production and innovation. At the same time, falling prices are also a positive incentive for consumers, encouraging greater consumption. For most markets, prices are able to balance the costs of production with the desires of consumers in order to create the right amount and the right type of goods and services. Changes in prices alter these incentives for both producers and consumers, which leads to changes in market outcomes.

There are instances, such as with the price system for antibiotics and antimicrobials, where inefficiencies arise. In such cases, policy reforms must carefully evaluate the impediments and, ideally, counter these impediments with the right type of incentives so that market prices are once again able to balance costs with the desires of consumers.

Due to the different impact from positive incentives and negative incentives, the appropriate use of policies that create positive incentives will differ from the appropriate use of policies that create negative incentives. When applied correctly, positive incentives can help counterbalance impediments that are discouraging a desired activity, and negative incentives can help counterbalance impediments that are encouraging an excessive amount of an activity.

With respect to antibiotics and antimicrobials, the appropriate policies will leverage positive incentives because the goal is to encourage an activity – the development of new drugs. Of course, care must be taken when implementing these policies. Poorly defined or overly generous positive incentives can enable people to obtain the positive reward without fulfilling the spirit of the incentive.

SUCCESSFULLY INCENTING PHARMACEUTICAL INNOVATION

While reforms are necessary, the current pharmaceutical regulatory environment reasonably addresses the inefficiencies that arise due to the conflicting needs of incenting pharmaceutical innovation and incenting market competition to help improve overall drug affordability. Potential inefficiencies arise because it is expensive to develop an innovative drug, but it is relatively cheap, and requires significantly less risk, to produce a drug once the development costs have been paid.

As documented in Winegarden (2015), the typical research and development (R&D) process to create one branded pharmaceutical drug:

- Requires 10 to 15 years to complete;
- Requires total capital costs between $1.6 billion and $17.2 billion, based on estimated research costs between $500 million and $5.5 billion; and,
- Entails a failure rate for introducing a new drug as high as 98.4 percent.

Clearly, developing a new drug takes a long time, costs a lot of money, and is fraught with risks. Due to the low cost of producing a medicine that has already been developed compared to the high cost of developing a new medicine, an imitator firm, who does not have to cover any of the costs of capital associated with developing the new drug, would always be able to profitably produce a new medicine cheaper than an innovative firm. The result would be no incentive for innovator firms to develop new drugs and pharmaceutical innovation would come to a standstill.

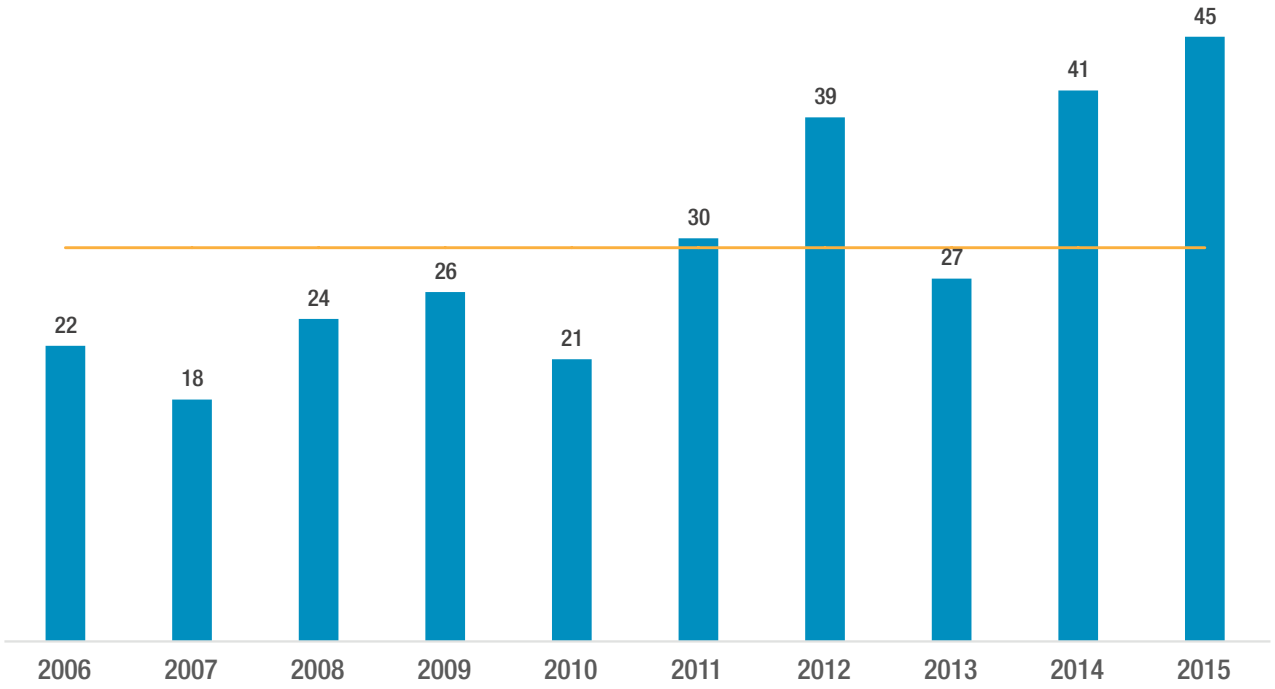
Based on the number of innovative medicines approved by the FDA each year, it appears that the policy of creating and enforcing patents has successfully encouraged the creation of many needed, and innovative, medicines.

To correct for these disincentives against innovation, drug innovators are provided an opportunity to cover their costs of capital via a period of temporary market exclusivity via a patent over the new medicine. The effective patent life of a new drug is currently around 11½ years – the effective patent life is defined as the time period that the developer holds the patent rights over the new medicine and the FDA has approved the new medicine for sale to the consumer. Within this 11½ year period of market exclusivity, the developer of an innovative drug has the ability to sell the medicine at a price high enough to recoup the billions of dollars of capital costs incurred.

Importantly, the temporary market exclusivity position only provides these firms with an opportunity to cover their costs of capital – the patent does not ensure that the firms' costs of capital are recovered. Additionally, it is important to note that pharmaceutical companies make pricing decisions based on market conditions and the product's value added. However, like any company, the prices set by a pharmaceutical company, and its subsequent revenues, must be sufficient to cover all costs – including the costs of capital. If this can be achieved, then the company stays in business. If this cannot be achieved, then the company's operations will cease.

With respect to incenting the development of new antimicrobial medicines, the key question is whether, broadly speaking, the current patent system sufficiently incents the development of new innovative drugs. And, based on the number of innovative medicines approved by the FDA each year, it appears that the policy of creating and enforcing patents has successfully encouraged the creation of many needed, and innovative, medicines, see Figure 1. Figure 1 illustrates that between 2006 and 2015, an average of 29 new innovative drugs were approved each calendar year. In 2014 and 2015, the number of new innovative drugs introduced were at 10-year highs; during each year more than 40 new therapies were introduced.

Figure 1
Novel Drug* Approvals per Calendar Year
2006 through 201



* Drugs include new molecular entities and new biologic license applications
Source: Food and Drug Administration

In 2016 alone, novel therapies were introduced to treat patients with muscular dystrophy, glycemic control, all six major forms of hepatitis C, and the most common type of bladder cancer.[1] Nearly one-half (47 percent) of the novel drugs were to treat rare diseases, which is important to note because the successful incenting of drug development for rare diseases has important lessons for incenting the development of drugs effective against AMR. Furthermore, these novel introductions do not include the hundreds of other new medications that, while perhaps not a novel therapy, were improvements to, or variations on, existing products. These successes illustrate that when there are no impediments unique to a drug class, the potential profits enabled by the current market exclusivity system are sufficient to incentivize pharmaceutical innovation.

However, as is the case with antimicrobial (particularly antibiotic) medicines, some innovative drug classes face unique impediments that sufficiently reduce the expected profit potential such that the current patent system is no longer sufficient to incent innovation.

THE PROBLEM OF INADEQUATE RETURNS TO ANTIMICROBIAL RESEARCH AND DEVELOPMENT

Incentivizing the development of drugs that can address the growing problem of AMR is problematic because, under the current patent system, the financial costs and risks of failure for developing antimicrobial medicines are too high relative to the revenues that can be earned, thereby creating a strong financial disincentive against developing these drugs. Antimicrobial medicines are not unique in facing such financial obstacles, however. Other drugs faced financial dis-incentives that similarly thwarted research and development until effective policies counterbalanced these obstacles.

Orphan drugs, or therapies that are developed to treat rare conditions, exemplify the problem, and potential solutions. In the U.S., a rare condition is typically defined as a disease that affects less than 200,000 people. The small population that can benefit from the development of an orphan drug, when coupled with the fact that the drug development costs are not necessarily any less (and could be more), limits the ability of companies to cover their costs of capital when developing drugs that treat rare diseases. Therefore, it was often financially infeasible to develop drugs to address rare diseases.

The Orphan Drug Act (ODA) of 1983 changed these incentives. The ODA improved the incentives to develop orphan drugs by offering longer market exclusivity, enhanced tax credits, and lower regulatory costs. These market reforms used positive incentives to improve the otherwise unfavorable potential profits from trying to develop an orphan drug. By improving the potential profit opportunity, the ODA is generally viewed as having successfully increased the amount of research and development that was devoted toward rare diseases and, ultimately, increased the number of orphan drugs that were developed to treat people with rare conditions, which was the desired activity. According to a 2013 report by PhRMA, "over the last 30 years, more than 400 medicines representing 447 separate indications have been approved to treat rare diseases, compared to fewer than 10 in the 1970s."[2] Without the ODA, it is generally viewed that the enormous increase in the drugs to address rare diseases would have otherwise been ignored.

There is a direct parallel between the success of the ODA to incent research into orphan diseases, and the problem of incenting the development of antimicrobial medicines. First, due to the appropriate medical protocol for using antimicrobial medicines that are effective against AMR, the potential revenue stream from selling a new antimicrobial medicine is inadequate to cover the expected capital costs. This financial problem arises because the greater the use of antimicrobial drugs, the greater the chances are that bacteria, viruses, fungi, and parasites will develop resistance to these drugs – it is the normal process of biological evolution. Therefore, once a drug that can effectively kill the resistant microorganisms has been developed, the ideal strategy is to not use it widely as a first-line of defense against the microorganisms. Instead, current drugs should be used to address the non-AMR infections, and then only when necessary, should the new drug be used to specifically address the drug-resistant microorganisms.

In short, medicines effective against AMR should be used sparingly in order to minimize the opportunity for microorganisms to develop resistance to these new medicines. Sparingly using new medicines, particularly during the limited time when the new branded drugs are on patent, limits the potential financial return from developing new drugs that will effectively treat the bacteria, viruses, and fungi that have developed resistance to the currently available medicines.

Second, according to the International Federation of Pharmaceutical Manufacturers, antibiotics are prescribed for a relatively short period of time – the prescription's duration is measured in days or weeks, the time it takes to kill the infection, rather than in years as is the case with other potential innovations. The shorter prescription time also limits potential antibiotic sales and consequently potential revenues.[3]

Third, the development costs for new antibiotic and antiviral therapies will likely be higher because the clinical trials require a highly selective patient population (e.g. those patients who are afflicted with the resistant microorganisms). There are simply fewer of these patients available, therefore, this requirement makes the clinical trials more difficult to carry out. There are additional requirements that further increase the costs of running a clinical trial for antibiotics and antivirals. Viable medicines already exist to treat infections from microorganisms, therefore it would be unethical to give control group patients who suffer from serious infections placebos instead of using existing medications. Using existing medications means that the clinical trials will "need to use a more challenging [and more expensive] (non-inferiority) design for trials of new antibiotics".[4]

Finally, despite the higher value of new antimicrobial medicines relative to current therapies, companies do not have the ability to increase their prices sufficiently to fully reflect this higher value.[5]

Due to the confluence of all of these factors, the ability of pharmaceutical manufacturers to cover their cost of capital is diminished. The diminished ability to cover the costs of capital dis-incents the development of new antimicrobial drugs (particularly new antibiotic drugs that are effective against gram negative bacteria). The estimates of antibiotics' potential return relative to other medicines confirm these disincentives.

The potential returns from medicines are often measured based on their expected net present value (NPV). The NPV calculation adjusts the value of the costs that will be spent on research and development over time, and the revenues that will be earned from selling the medicine over time, to account for the time value of money. Accounting for the time value of money is important because receiving a dollar today provides options that are not available if the money is received tomorrow. Therefore, a dollar received today is worth more than a dollar received tomorrow. The opposite logic holds for expenditures.

The NPV calculation accounts for the value difference between receiving a dollar today and receiving a dollar tomorrow by translating all of the costs that are spent on the drug's research and development, and all of the income that is earned selling the drug, into a single dollar number that represents the value of those income streams today. It provides a reliable benchmark from which different projects that have different income and cost profiles can be accurately compared.

As cited in Sharma and Towse (2011) and Mossialos et al. (2009), the risk adjusted net present value of developing antibiotic medicines is estimated to be approximately $100 million. Such a return pales in comparison to other potential investments. For example, the risk adjusted net present value for oncology medicines is $300 million; for musculoskeletal medications the risk adjusted net present value is $1.15 billion.[6] Furthermore, updated research from DiMasi et al. (2016) has estimated that the development and capital costs of drugs has continued to rise, indicating that the current estimated NPVs are likely even higher.[7]

Spellberg (2014), citing a study from the London School of Economics, similarly noted

> that, at discovery, the net present value (NPV) of a new parenteral antibiotic agent was minus $50 million. … By comparison, at discovery, the NPV for a new arthritis drug has been estimated to be positive $1 billion. Given these economic realities, it is easy to understand why for-profit companies, which have a fiduciary responsibility to increase shareholder value, have increasingly shunted R&D money away from antibiotics and toward other drug types.[8]

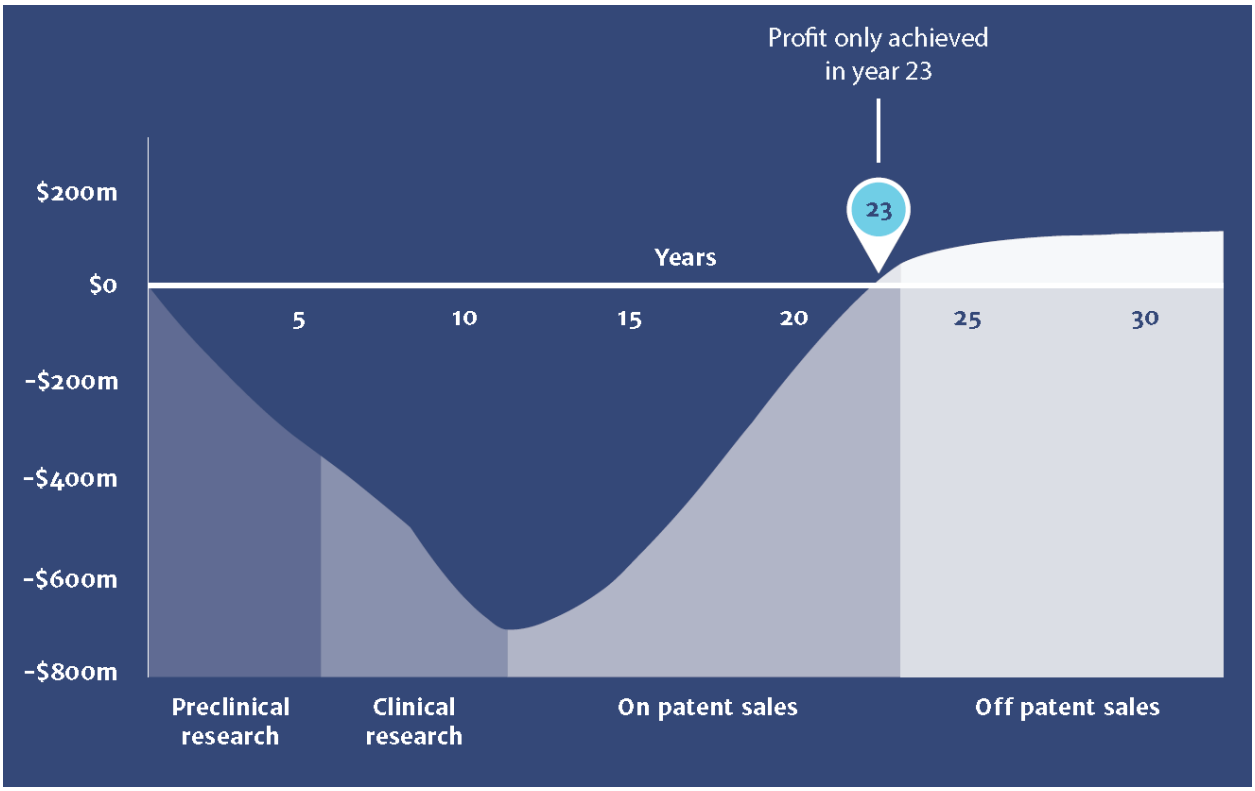
Also indicating an inadequate return for antibiotic research, Mossialos et al. (2009) noted that "the numerous challenges unique to the antibiotics market have significantly reduced the market revenues for pharmaceutical companies investing in this therapeutic area. Most antibiotics generate annual revenues of only US $200–$300 million, while the costs of bringing any drug to market are currently estimated to be US $400–$800 million per approved agent."[9]

Additionally, because antibiotics have such a relatively low, or even negative, net present value, the risks to profitability from FDA regulatory changes is greater. For instance, Power (2006) estimated that stricter regulatory requirements from the FDA can push "the overall expense of developing a new antibiotic to a level that cannot be justified economically."[10] As an example, Power (2006) estimated that a regulatory change by the FDA, which is now implemented on a case-by-case basis due to its costs, reduces the net present value of developing an antibiotic from $100 million to approximately $35 million.

Antibiotic development costs are also higher. As noted in a 2011 conference sponsored by the Pew Health Group (Pew), the Infectious Diseases Society of America (IDSA), and the Pharmaceutical Research and Manufacturers of America (PhRMA) "on average, manufacturers must pursue roughly 15 leads, or drug development candidates, to ensure one successful approved drug. However, an analysis of a GSK program showed that the development of one successful antibiotic required 72 promising compounds. It 'doesn't look very attractive for any company to move back into this area or to expand their effort.'"[11]

O'Neill (2015) summarizes the expected profit potential by examining the cumulative expected profit potential from antibiotic research, reproduced as Figure 2. Based on the analyses from the *Review on Antimicrobial Resistance*, they estimate that investing in new antibiotics will only turn a profit 23 years following the beginning of the research process, which is toward the end of the typical patent lifespan. Additionally, the profits earned are small, particularly compared to the cumulative costs required.

Figure 2
Cumulative Profit Potential from Investing in Antibiotic Research[12]



Reproduced from the O'Neill Report (2015)

In summary, without policy changes, it makes no financial sense for a pharmaceutical manufacturer to devote scarce R&D resources toward antibiotics because the current risk adjusted net present value is simply too small.

EVALUATING THE PROPOSALS TO INCENT AMR RESEARCH

The low expected NPV for antibiotic medicines contrasts starkly with the high expected NPV for many other innovative drugs. This discrepancy, when coupled with the continued innovation for these cutting-edge drugs, indicates that, unlike antibiotic and antimicrobial medicines, there are strong financial incentives to develop many other innovative medicines.

As discussed earlier, the financial returns are enabled by the current patent system that sufficiently incents the pharmaceutical industry to produce novel innovations that improve health outcomes across a wide variety of disease areas. These incentives are insufficient for antimicrobial, and particularly antibiotic medicines, however, due to the medically appropriate strategy of using these medicines sparingly once they have been developed. When coupled with the other unique factors that raise the costs of developing antimicrobials and reduce the potential revenues from selling antimicrobials, the expected profit potential from developing new antibiotic and antimicrobial drugs is simply insufficient.

It is also generally agreed that, without new innovations, the health threats posed by the AMR problem will grow; therefore, incenting the development of antimicrobial, particularly antibiotic, therapies is an important policy reform. And, in response to these problems, the GAIN (Generating Antibiotic Incentives Now) Act was signed into law on July 9, 2012.[13] The GAIN Act provided an additional 5 years of market exclusivity to "qualified" antibiotics, as well as expedited regulatory review. While generally viewed as beneficial, it is also generally viewed that the GAIN Act was insufficient.[14]

Given the large number of incentive proposals that will impact the market differently, it is important to rigorously evaluate the merits and weaknesses of the different approaches.

Many different proposals have been proffered to further incent the development of antimicrobial medicines. In reviewing these proposals, Renwick et al. (2016) identified 47 different incentive strategies.[15] But, all policies to incent development are not equally effective. The observed behavioral changes following changes in incentives will vary depending on the type of incentive that is applied. Since the goal is to encourage the development of antibiotics and antimicrobials, governments should be relying upon well-designed positive incentives to increase the expected risk-adjusted net present value from investing in antimicrobials. This goal is generally achieved by policies that either increase the returns from producing these drugs, or lower the costs of developing these drugs.

The incentives that increase the return for companies that invest in antimicrobial research are referred to as pull incentives. Pull incentives increase the expected NPV by increasing the revenues an innovator can expect to earn by successfully developing antibiotics or other antimicrobials. Pull incentives reward outcomes, such as the successful development of a new drug. In light of the medical need to use any new antibiotic or antimicrobial as a second or third line of defense against infections, a common theme across pull incentives is to "delink" the profitability of developing new antimicrobials from the total volume of sales.

The incentives that attempt to lower the costs of developing antimicrobial drugs are generally referred to as push incentives. Push incentives create rewards based on research inputs rather than pharmaceutical outcomes. Push incentives, therefore, encourage greater research, but whether that research successfully develops a new medicine is unknown. The logic behind push incentives is that by lowering the necessary research costs, the NPV from investing in new antibiotics or other antimicrobials will increase. The higher NPV should then induce greater investment into these research areas and, ultimately, into the introduction of more medicines that can address the AMR problem.

Given the large number of incentive proposals that will impact the market differently, it is important to rigorously evaluate the merits and weaknesses of the different approaches. Table 1 summarizes the typical incentive proposals that researchers have identified as able to encourage the development of antibiotics and other antimicrobials. Table 1 combines together similar proposals under broader categories in order to keep the number of proposals evaluated manageable.

Table 1
Proposed Incentives to Encourage the Development of Antimicrobial Medicines

INCENTIVE	STRENGTHS	WEAKNESSES	COMMENTS
Pull Incentives			
Lottery / Prizes	Delinks innovators' profitability from sales volume and increases the expected NPV	Incentives not necessarily connected to cost of capital; requires large investment from governments, and imposes significant administrative burdens	
Guaranteed volume purchases	Delinks innovators' profitability from sales volume and increases the expected NPV	Incentives not necessarily connected to cost of capital; requires large investment from governments	
Licensing patents to government/government buyout of license	Enables innovators' to receive present value of the new medicine, while eliminating the incentive to increase volume	Valuation issues could arise; requires large investment from governments	
Expanded data exclusivity	Expands innovators' opportunity to recoup costs of capital, raising expected NPV	Conflict between sales and profits remains	Data exclusivity disallows the FDA from relying on an innovator's safety and efficacy data for approving a competitor's products enabling the innovator to exclusively benefit from its investments in R&D.
Expanded market exclusivity	Expands innovators' opportunity to recoup its cost of capital, raising expected NPV	Conflict between sales and profit remains	Market exclusivity disallows competitive products that rely on the same innovation.
Transferable expanded market / data exclusivity	Expands innovators' opportunity to recoup its cost of capital based on the most profitable opportunity, increasing expected NPV more than simple expanded market /data exclusivity, while also delinking sales and profits	Cross subsidization of antibiotic development	
Enable more effective market pricing	Price premium incents innovators to undertake research, and dis-incents over-use (over-use risks losing effectiveness and thus price premium)	Issues of affordability and payer participation arise	Medicines that address AMR microorganisms have a higher value, in an efficient market, pricing reflects higher value.
Regulatory review vouchers	Accelerates realization of product revenues and potential competitive position, thus improving NPV		A regulatory review voucher provides innovators with a "FDA priority review voucher" to be redeemed for a future medicine.

Push Incentives			
Reduction in regulatory burdens	Lowers innovators' cost of developing drugs		If regulatory burdens can be lowered without harming safety or efficacy, a win-win reform. Sometimes referred to as Lego-Regulatory incentives.
Subsidize research (e.g. The Infectious Disease Finance Facility, AMR Innovation Fund, Public Private Partnerships, and Options Market for Antibiotics (OMA))	Lowers innovators' cost of developing drugs	Subsidizes all research (input) regardless of efficacy (or successful outcomes); requires large investment from governments	The later the stage of research that is subsidized, the more closely the subsidy targets outcomes rather than inputs, however due to time value of money, the later the stage the smaller the impact on increasing expected NPV.
Tax credits	Lowers innovators' overall cost of R&D	Targets input, not outputs; requires large investment from governments	
Other Policies			
Antibiotic usage tax	Reduces the use of antibiotics	The tax reduces affordability; the tax is a negative incentive that reduces expected NPV and diminishes incentives to innovate	Revenues from these proposed taxes are typically earmarked toward funding research subsidies. Usage taxes are the only major proposal that relies on a negative incentive to change behavior -- when trying to incent a behavior (not discourage a behavior), positive incentives are more beneficial.
"Pay or play"	Incents more resources to be devoted toward AMR research	The tax is a negative incentive that diminishes overall incentives to innovate. For AMR research, it will lead to an inefficient allocation of research resources that encourages low-quality research	The O'Neill Report proposes a 0.5% tax on global revenue on pharmaceutical companies that do not engage in AMR R&D.

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Pull Incentives

Starting with the pull incentives, lump sum payments (or what is sometimes referred to as a lottery or research prize) are often promoted as an effective policy for increasing the potential returns from investing in antibiotics and antimicrobials. Lump sum payments offer a set dollar payment to innovating companies that successfully develop an antibiotic or other antimicrobial.

Similar to lump sum payments, are proposals that establish guaranteed volume purchases. These incentives guarantee innovative firms a set sales level of the new medicine regardless of how many prescriptions are actually written (these agreements can also include private sector licensing agreements). Instead of providing a known payment, guaranteed volume purchases create certainty with respect to a known quantity of sales.

There are also proposals where the innovative firms will either license the patents to the government, or the government will buy out the patent from the innovative firms. In either case, these buyout proposals enable an innovator firm to receive the present value of the new medicine upfront, increasing their potential returns.

All three of these proposal categories create new positive incentives and provide potential innovators with a known financial return should their research efforts be successful. By offering certainty of revenues, lump sum payments, guaranteed volume purchases, and government licensing buyouts reduce overall financial risks, increase the expected net present value from developing antibiotics, and de-link revenues from sales.

However, these proposals are constrained by the need to establish the appropriate payment levels or guaranteed sales level. For instance, O'Neill (2015) assumes that the research costs for developing a new antibiotic are around $300 million to $400 million, plus marketing costs of around $400 million.[16] Therefore, O'Neill (2015) concludes that the lump sum payments would need to be between $1 billion and $1.3 billion in order to cover development costs, including the costs of failure.[17] Should the actual development costs exceed these levels, and based on the current literature it is likely that the costs will significantly exceed these levels,[18] then the positive incentive from a lump sum payment may be insufficient to adequately incent development. A similar problem plagues the guaranteed volume purchases and licensing buyout proposals. Additionally, the large one-time payments require a commitment level that many governments may be unwilling to bear, which raises serious questions regarding the sustainability of these expenditure programs.

Similar to the Orphan Drug Act, other proposed pull incentives will improve the exclusivity period for antibiotics and antimicrobials in order to increase the potential revenue that an innovative firm can expect to receive. The expanded exclusivity can apply to the market or to the safety and efficacy data.

Market exclusivity prevents competitive products that rely upon the patented innovation from coming to market. By providing an innovative firm an opportunity to solely profit from its innovations, market exclusivity provides an opportunity to these firms to recoup their capital costs, raising their expected NPV. Data exclusivity refers to the safety and efficacy data that an innovative firm produces through its expensive drug trials. During a period of data exclusivity, only the innovative firm that created the safety and efficacy data may use that data with the FDA. Without data exclusivity, competitors can rely upon the innovative firm's safety and efficacy data when petitioning the FDA for approval of its drug. With data exclusivity, this common practice is disallowed and only the innovative firm is allowed to benefit from its research investments. With data exclusivity, any competitive product can be introduced into the market at any time, but the catch is that any firm that wants to introduce a new product must also spend the money to ensure that its product is safe and effective. Therefore, the cost structures of the two competing products will be more similar.

Expanded exclusivity, either market or data, increases an innovator's opportunity to recoup its costs of capital, further increasing the expected NPV from developing antibiotics. Another strength of expanded exclusivity is that it does not require any additional government expenditures. This improves the sustainability of the programs as it does not require political leaders to continually justify making large expenditure payments. An important weakness of expanded market exclusivity and expanded data exclusivity is the failure of these programs to de-link the innovator's revenues from the sales of antibiotics.

Enabling the innovative firm to transfer the expanded exclusivity to its most valued opportunity (transferable expanded market / data exclusivity) addresses this de-linkage problem. Transferable expanded exclusivity enables an innovating firm to apply the expanded exclusivity to its most profitable opportunity, which could also be with another firm assuming the transferable expanded exclusivity vouchers are saleable to another company. Enabling the exclusivity to be transferable creates two additional benefits. First, the expected NPV is enhanced more than with nontransferable expanded market or data exclusivity because the exclusivity can be applied where it is most profitable. Second, by making the exclusivity benefits transferable, the revenues for the innovator and the sales of antibiotics are successfully de-linked.

An oft-cited concern with respect to transferable expanded exclusivity is the issue of cross-subsidization – prices in an unrelated pharmaceutical market are higher due to the development of an innovative antibiotic. However, these concerns are overblown because the practice of successful drugs cross-subsidizing failures is typical in the pharmaceutical industry, and the payer (private health insurer or the government) in many instances will be the same. Furthermore, such concerns pale in comparison to the benefits of both delinking antibiotic sales and enabling a more *market-based* process to provide innovators with an opportunity to cover their cost of capital.

Expanded exclusivity, either market or data, increases an innovator's opportunity to recoup its costs of capital, further increasing the expected NPV from developing antibiotics.

As an alternative to policy-induced incentives, another approach would enable a more effective market pricing structure such that the value added created by new antibiotics can be appropriately priced. If the health care market were efficient, then the higher value that these new drugs create would command a price premium relative to other antimicrobials that would simultaneously incent research and dis-incent over-use (over-use would be dis-incented because it would unnecessarily risk microorganisms gaining resistance to the new antimicrobials, and thus unnecessarily risk the price premium the new drug would be receiving).

However, more effective market pricing may raise issues of affordability and payer participation. Additionally, it is unlikely that an efficient market-based pricing system could be established within the current highly regulated global health care markets that include strict price controls.

The final pull incentives are reductions in the current regulatory burden. These reforms are sometimes categorized as a push incentive, and sometimes referred to as a Lego-Regulatory reform. Proposed regulatory reductions include reforms such as granting the innovative drug priority review, or altering the testing requirements for innovative antimicrobial drugs. Reducing the regulatory burden is particularly valuable for antimicrobials due to the unique attributes of the target population that increases the time and expense required to get these drugs approved. A related incentive offers a reduction in regulatory costs via a transferable "priority review voucher" that can be redeemed for a future medicine – an incentive that is similar to the transferable expanded exclusivity period, except the transferability reduces costs on another potential medicine.

The purpose of the regulatory reforms is to both reduce the costs of developing drugs without impacting the safety or efficacy of the innovation and expand the effective market exclusivity of these innovative drugs. And, clearly reductions in regulatory costs that do not compromise safety or efficacy are clearly a win-win reform—innovative medicines are brought to market quicker, and due to the lower costs the expected NPV on these drugs are higher. Regulatory review vouchers expand these benefits by connecting the potential lower regulatory costs to the innovators most valued use.

Push Incentives

An oft-proposed push incentive is to increase spending on basic research or more subsidies to private researchers, either directly or through the establishment of Public Private Partnerships. Providing innovator firms with tax credits is a related proposal that indirectly subsidizes research by lowering the tax bill of those organizations that devote resources toward the development of antimicrobials.

There are many proposals to increase the number of research subsidies available for antibiotic or antimicrobial research. For example, the *2014 Report to the President on Combatting Antibiotic Resistance* calls for $800 million in federal expenditures to help incent the commercial development of new antibiotics.[19] As another example of a proposed push incentive, the European Investment Bank (EIB) and the European Commission (EC) have proposed a funding mechanism referred to as the Infectious Disease Finance Facility. According to Brogan and Mossialos (2016), "This facility will utilize risk sharing loans that will only require repayment if they result in a marketable product. If successful antibiotics pay money back into the fund, this will increase the overall size of the fund and allow further rounds of funding. The EC and EIB predict at least a 5x multiplier effect due to the requirement that grant recipients or other donors match at least half of the required funds for the project. While the exact terms of such loans have yet to be determined, each project applying for funding must have completed pre-clinical testing."[20]

The goal of these research subsidies is to increase the NPV of developing new antimicrobials by lowering the cost of developing these needed drugs. The downside to the different forms of research subsidies is that it targets research regardless of its ultimate impact. While research is a necessary input to developing the needed antimicrobial medicines, it is not the end in itself. The ultimate goal is the creation of new antimicrobial medicines that are effective against AMR. The separation of the subsidy from the ultimate goal raises the possibility of wasteful research efforts that do not produce (either directly or indirectly) more antimicrobial medicines.

This downside can be minimized by targeting subsidies toward later stage research benchmarks. The later the stage of research that is subsidized, the more closely the subsidy targets the desired outcome (the development of needed antimicrobials) rather than inputs (research efforts). This targeting comes with a cost, however, due to time value of money. Subsidizing later stages of development implies that the research subsidies will be received later in time. Receiving the money later means that the subsidies will have a smaller present value and, consequently, a smaller impact on increasing the medicines expected NPV.

Additionally, subsidies require large investment from governments. These expenditures may be unaffordable, or require the governments to forgo other expenditure opportunities. While investments in subsidizing antimicrobial medicines may be a higher-valued use of government health research dollars, such expenditures do impose an opportunity cost that should be taken into account.

Other Policies

The need to fund government expenditures raises a proposal that is sometimes suggested with respect to the AMR problem – a tax on antibiotics, generally for the purpose of funding the research subsidies and tax credits. Imposing a tax on antibiotics will raise the price to consumers, and lead to a reduction in the use of antibiotics. To the extent the marginal users are the inappropriate users, this reduction in consumption is beneficial. However, it is unknown whether the marginal users are the inappropriate users. Additionally, there are other negative impacts from imposing such a tax that far outweigh any potential benefit.

The ODA increased market exclusivity and lowered regulatory barriers to improve the incentives to develop drugs for rare diseases.

A tax is a negative incentive, and the burden from this negative incentive is generally not solely borne by consumers. They are also borne by producers. Imposing an antibiotic tax reduces the revenues that an innovator can expect to earn from developing a new antimicrobial and, consequently, reduces the antimicrobial's expected NPV. This impact counteracts the incentives from all of the other pull and push incentives that may be applied, and diminishes the incentive for innovation. Additionally, an antibiotic tax reduces affordability for consumers, which is an important concern, particularly in less wealthy nations.

Another tax proposal suggested in the *O'Neill Report* is a tax on global revenues on those pharmaceutical companies that do not engage in a sufficient amount of AMR research and development. This "pay or play" tax, as proposed in the *O'Neill Report*, taxes pharmaceutical companies 0.5% on their global revenue.

The purpose of the "pay or play" tax is to encourage more private sector research, or raise revenues that can be devoted toward public AMR research from those companies that do not. The major flaw in this idea is the use of a negative incentive to try to encourage an activity. The negative incentive will discourage companies from not investing into AMR research. However, because the research expenditures were forced, and are being performed only to avoid the tax penalty, there is a greater chance that these resources will be used inefficiently and, thus, lead to low quality research. A punitive tax on industry is not an efficient method for incentivizing high quality research.

CONCLUSION

Antimicrobial resistance is a growing global health threat, and despite the medical value that new antibiotics and antimicrobials could offer, adverse incentives are discouraging the development of these needed medicines. Policies that reduce, and ideally eliminate, these adverse incentives are, consequently, needed.

However, all policies are not equally effective. The successful incenting of research from past policy interventions, such as the Orphan Drug Act, provides important lessons. The ODA increased market exclusivity and lowered regulatory barriers to improve the incentives to develop drugs for rare diseases. These policy changes enabled the typical pharmaceutical market incentives that encourage pharmaceutical innovation to incent innovation for rare diseases.

Applying these lessons, transferable expanded market exclusivity and transferable expanded data exclusivity are promising pull incentives that achieve two important goals. First, by making the expanded exclusivity transferable, the profitability of investing in antibiotic and antimicrobial research is delinked from the sales volume of antibiotics and antimicrobials. Delinking profitability and sales enables innovators to earn a profit while still following the medically prudent strategy of using the latest innovations as a second- or third-line of defense against infections. Second, the transferable exclusivity connects the opportunity to earn a profit for investing in novel antibiotics and antimicrobials to the successful market in other drug areas where innovators have been able to successfully cover their costs of capital.

Lessening the regulatory barriers without harming safety or efficacy, another lesson from the ODA, is another important reform that can help reduce costs and, consequently, increase the expected NPV from investing in new antibiotics and antimicrobials. These regulatory cost reductions can apply both to the development of antibiotics and antimicrobials. They can also be in the form of a transferable priority review voucher that will enable an innovator to apply the regulatory cost savings where it is most valuable.

Push incentives that allocate research resources toward antimicrobials, or reduce the research costs for innovative firms, also have merit. Care must be taken when applying these incentives, however. The combination of subsidies and tax credits should account for the impacts different types of subsidies will have on incentives and costs. An overemphasis on early stage research may lead to less productive research, whereas an overemphasis on late stage research may increase the project's NPV too little. The ideal subsidies will balance these considerations. Additionally, proposals to levy antibiotic taxes to fund new research efforts impose more harm than good. Such negative incentives reduce the expected NPV from innovative medicines diminishing the incentive for new antimicrobials.

Overall, there are too many obstacles inhibiting the development of antibiotic and antimicrobial medicines despite the medical need. Countermeasures that improve these incentives are necessary. The overarching goal of these policies should be to improve the expected net present value from investing scarce resources into antibiotic research.

ENDNOTES

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