

Incentives to stimulate antibiotic innovation:

The preliminary findings of DRIVE-AB

DRIVE-AB: Transforming the way policymakers stimulate innovation, responsible use and global access of novel antibiotics to meet public health needs

The problem:

Dangerous bacteria are becoming resistant to antibiotics faster than new antibiotics are being developed to stop them.

Resistance to antibiotics increases with their use.¹ This is a natural evolutionary process whereby bacteria adapt so that the antibiotic is no longer effective. When such resistant bacteria cause health problems, another antibiotic will be needed to treat the infection. Antibiotic resistance becomes a problem when bacteria become resistant to many or all drugs so that there are few or no effective antibiotics to treat an infection. Since the late 1980s there has been a lack of antibiotic innovation. No new classes of antibiotics meeting unmet needs have reached the market in decades.^{2,3} There are several reasons why the current R&D portfolios of pharmaceutical companies are insufficient to meet current and future public health needs. Antibiotic discovery is technically challenging, and it is not sufficiently profitable as compared to developing drugs for other disease areas. The market is fragmented into segments that are small, low priced and unpredictable. A company's return on investment for developing a novel antibiotic is significantly lower than other competing medicines. This creates an upstream knock-on effect, where small to medium enterprises and academics focused on antibacterial research may also struggle to secure financing.

The consequence is that life-threatening, untreatable infections are emerging, leading to significant morbidity and mortality consequences which also jeopardize modern medicine's ability to safely perform other interventions such as routine surgeries and cancer treatment.

The interdependencies:

Stimulating antibiotic innovation alone will not solve the problem. Promoting sustainable use and greater access are also key.

Antibiotic resistance is a global problem and providing access to effective antibiotics is a public health priority. However, if these antibiotics are used inappropriately, both in animals and humans, higher numbers of drug-resistant bacterial infections will occur, increasing the need for innovation. It is more cost-effective to maintain the effectiveness of the world's existing antibiotics than trying to continually replace them. Innovation will always be necessary, but the pressure to find entirely new antibiotics can be reduced by working in parallel to prolong the efficacy of existing antibiotics.

The opportunity:

New incentives, coupled with provisions for sustainable use and equitable access, are needed to stimulate antibiotic innovation.

The research project, DRIVE-AB (i.e., Driving reinvestment in research and development for antibiotics and advocating their responsible use, www.drive-ab.eu), is a consortium of 16 public sector partners and seven pharmaceutical companies supported by the European Innovative Medicines Initiative (IMI). DRIVE-AB is tasked with defining responsible use of antibiotics, identifying the antibiotic-related public health priorities, calculating the societal value of having new antibiotics available for these priorities, developing and costing new economic models to promote the desired antibiotic innovation, and sustainable use of the resulting, novel antibiotics. The purpose of the project is to transform the way policymakers stimulate antibiotic innovation and to ensure that these new antibiotics are used sustainably and available equitably.

DRIVE-AB's shortlist of incentives:

Stimulating greater antibiotic innovation is a complex and multifaceted problem, and it is unrealistic that one solution can effectively stimulate all necessary innovation. Therefore, DRIVE-AB has shortlisted a set of solutions to stimulate different types of R&D and provide options for different health care systems (see table below).

Incentive/Model	Type ¹	Type of innovation stimulated	De-linkage ²	Promotes sustainable use	Promotes equitable availability
Grants: Non-repayable research funds	Push	Early phase research	n/a	Untested	Untested
Non-Profit Antibiotic Developer: An independent organization that manages and finances a portfolio of antibiotic discovery and development projects through to commercialization	Push	Incremental innovation and development with a higher risk profile	n/a	Strongly	Strongly
Diagnosis Confirmation Model: A dual-pricing model where a premium price is charged if the antibiotic is used for the entire course or a lesser price if the antibiotic is used first empirically and then promptly deescalated	Pull	Greater diversity of broad and narrow-spectrum antibiotics with significant improvements	No	Moderately	Weakly
Insurance Licenses: An annual license paid to a manufacturer to have access to a specific antibiotic, up to a specified volume	Pull	Rarely used, emergency antibiotics	Yes	Strongly	Weakly
Market Entry Rewards: A series of predefined lump-sum payments awarded to the developer after regulatory approval of an antibiotic meeting predefined characteristics	Pull	Most pressing public health threats	Yes	Strongly	Strongly

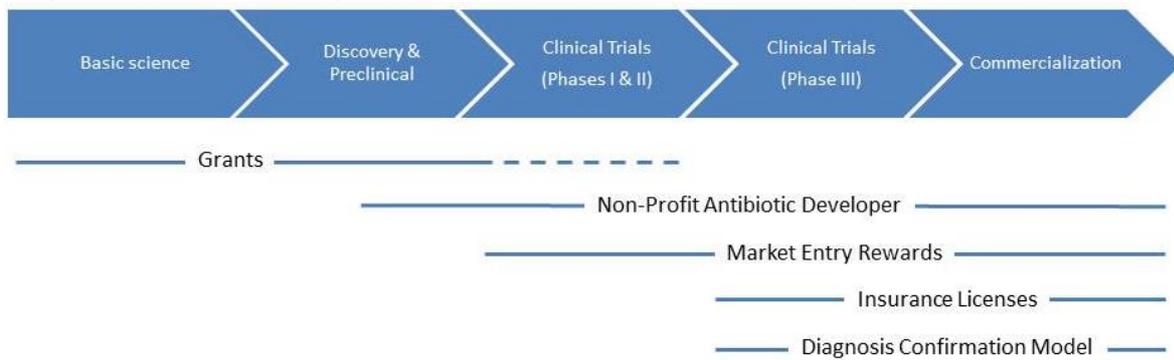
¹ Pull = developers are rewarded for specific results; Push = R&D costs are supported

² Delinkage = revenues are not linked to consumption

Each incentive/model is meant to stimulate different types of antibiotic innovation as well as different stages of the R&D process (see Diagram 1). They are designed to be complementary, but the pull incentives are mutually exclusive, i.e., the same antibiotic cannot be supported simultaneously by more than one pull incentive. Grants may be also necessary to support early phase

clinical trials. The impact of the pull mechanisms on traditional financing, like venture capital, needs to be assessed.

Diagram 1: Antibiotic R&D phases that each incentive/model is anticipated to stimulate



These incentives are a preliminary short-list. Each model has merits and is considered by the DRIVE-AB consortium to be worthy of further consideration, however these models do not necessarily meet all of the project objectives and should by no means be considered the final DRIVE-AB recommendations. DRIVE-AB is now gathering external feedback and will be simulating the impact of these incentives. Where insufficiencies are found, incentives will be modified or replaced.

Background

DRIVE-AB: Transforming the way policymakers stimulate innovation, responsible use and global access of novel antibiotics to meet public health needs

The problem:

Dangerous bacteria are becoming resistant to antibiotics faster than new antibiotics are being developed to stop them.

Resistance to antibiotics increases with their use.¹ This is a natural evolutionary process whereby bacteria adapt so that the antibiotic is no longer effective. When such resistant bacteria cause health problems, another antibiotic will be needed to treat the infection. Antibiotic resistance becomes a problem when bacteria become resistant to many or all drugs so that there are few or no effective antibiotics to treat an infection. The development of resistance is accelerated by the use of antibiotics in health care, food production, and by pollution of the environment due to release of antibiotic manufacturing waste.¹

Since the late 1980s there has been a lack of antibiotic innovation. No new classes of antibiotics meeting unmet needs have reached the market in decades.^{2,3} There are several reasons why the current R&D portfolios of pharmaceutical companies are insufficient to meet current and future public health needs. First, antibiotic discovery is technically challenging — the art of finding products that can kill bacteria without harming the patient remains dependent on fortuitous discoveries that come all too infrequently. Second, antibiotic development is complex, especially when the goal is to develop new drugs in advance of widespread emergence of resistance. Finally, and the core problem addressed by DRIVE-AB, is that antibiotic development is not sufficiently profitable as compared to developing drugs for other disease areas. The global USD 40 billion antibiotic market is fragmented into segments that are small, low priced and unpredictable. A company's return on investment for developing a novel antibiotic can be significantly lower than for other competing medicines (see box). Low and unpredictable revenues make companies more sensitive to R&D costs for antibiotics than in other therapeutic areas.⁴ As one measure of the challenges of this area, there were more than 25 large, pharmaceutical companies with active antibacterial drug discovery programs in 1980; today only four remain.⁵

Barriers to antibiotic investment

A company's return on investment for developing a novel antibiotic is significantly lower than other competing therapeutic areas due to:

- Many older and inexpensive antibiotics are still highly effective for most patients. Therefore, hospitals and primary care rationally prescribe proven, inexpensive antibiotics.
- The desire to preserve the use of novel antibiotics leads to slow initial uptake.
- Although the overall antibiotic market is large, it is fragmented into multiple markets by hospital specialty and resistance patterns. Thus, the markets for each of the different drugs can be comparatively small.
- The resistance rate of a particular pathogen is difficult to predict, resulting in high uncertainty of unmet need and future revenues.

Nevertheless, some Small and Medium-Sized Enterprises (SMEs) find opportunities in antibiotics. Yet, given the limited profitability of antibiotics, many of these companies face funding challenges, particularly for research that is "too applied" for science funders (i.e., not publishable) and "too basic" for venture capitalists (i.e., too risky). It is also difficult to get funding for the costly, later stage clinical trials. These knock-on effects continue upstream to impact academic competencies. Since

there are few career opportunities for students and scientists working in life sciences, there is a lack of expertise in basic infectious disease research and clinical microbiology.

The consequences:

Life-threatening, untreatable infections are emerging which also jeopardize modern medicine's ability to safely perform routine surgeries and cancer treatment.

In hospitals, infections caused by antibiotic-resistant bacteria may prolong hospital stays or even kill patients. The European Union estimates that 25,000 patients die every year from infections by antibiotic-resistant bacteria.⁶ Infections sometimes occur during health care interventions such as intra-abdominal surgery, organ transplants, and hip replacements, which have become 'routine' procedures. The availability of effective antibiotics makes performing these medical procedures less risky. A study examining the potential consequences of increases in antibiotic resistance on common surgical procedures and chemotherapy found that a 30% reduction in the efficacy of antibiotics used to prevent infections after these procedures would result in 120,000 additional infections per year in the USA alone.⁷

The interdependencies:

Stimulating antibiotic innovation alone will not solve the problem. Promoting sustainable use and greater access are also key.

Antibiotic resistance is a global problem, but far more people die today from a lack of access to antibiotics than from resistant infections. More than one million children die every year from pneumonia and sepsis, both of which are often treatable with inexpensive, older antibiotics.⁸ Increasing access to effective antibiotics is a global priority. However, if these antibiotics are used inappropriately, higher numbers of drug-resistant bacteria will occur, increasing the need for innovation.

Pharmaceutical innovation is time-consuming (at least 10-15 years from discovery to market), risky (approximately 80% of drugs in development fail) and expensive (from USD 250 million to more than one billion).⁹⁻¹³ Developing completely new antibiotics is scientifically complex. It is more cost-effective to maintain the effectiveness of the world's existing antibiotics than trying to continually replace them. Innovation will always be necessary, but the pressure to find entirely new antibiotics can be reduced by working in parallel to prolong the efficacy of existing antibiotics. Yet even a slow pace of innovation is not being achieved today. Recent pipeline reviews show that fewer than 40 antibiotic therapies are in development and of these only one is an entirely novel class.¹⁴

The opportunity:

New incentives, coupled with provisions for sustainable use and equitable access, are needed to stimulate antibiotic innovation.

The research project, DRIVE-AB (i.e., Driving reinvestment in research and development for antibiotics and advocating their responsible use, www.drive-ab.eu), is a consortium of 16 public

sector partners and seven pharmaceutical companies supported by the European Innovative Medicines Initiative (IMI). DRIVE-AB is tasked with defining responsible use of antibiotics, identifying the antibiotic-related public health priorities, calculating the societal value of having new antibiotics available for these priorities, developing and costing new economic models to promote the desired antibiotic innovation, and sustainable use of the resulting, novel antibiotics. The purpose of the project is to transform the way policymakers stimulate antibiotic innovation and to ensure that these new antibiotics are used sustainably and available equitably.

DRIVE-AB is not the only project evaluating incentives for stimulating greater antibiotic innovation. Most notably the UK Review on Antimicrobial Resistance, Chaired by Lord Jim O'Neill, has delivered a series of reports recommending a set of high-level actions needed not only to stimulate antibiotic innovation but also about to increase infection prevention and surveillance, examine alternative antibacterial technologies and improve rapid diagnostics.¹⁵ Its final report and recommendations were issued in May 2016. DRIVE-AB has worked in parallel to develop specific options and recommendations regarding governance and financing models as well as the necessary provisions to ensure sustainable use and equitable availability to novel antibiotics. DRIVE-AB's recommendations will be scrutinized by a broad range of stakeholders including policymakers, healthcare insurers (both national and private), medicines regulatory and reimbursement authorities, SMEs, national research funding agencies, academic research institutions, health technology assessors, and more. Although principally European in focus, DRIVE-AB will actively engage globally to ensure that its recommendations can integrate in the broader context of ensuring access to effective antibiotics and combatting resistance.

DRIVE-AB's shortlist of incentives:

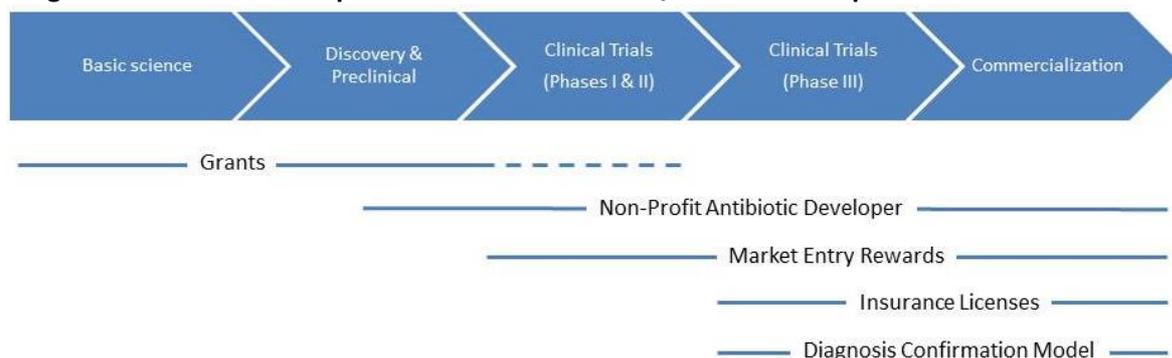
Stimulating greater antibiotic innovation is a complex and multifaceted problem, and it is unrealistic that one solution can effectively stimulate all necessary innovation. Therefore, DRIVE-AB has shortlisted a set of solutions to stimulate different types of R&D and provide options for different health care systems.

DRIVE-AB has extensively reviewed a large number of incentives designed to stimulate greater innovation. These include both those targeted to increase pharmaceutical innovation as well as those in other industries. Incentives can be classified as either "pull", meaning that developers are rewarded only if they provide specific results, or "push", meaning that R&D costs are supported prior to achieving specific results. After internal review and assessment of a long list of incentives, DRIVE-AB has shortlisted five incentives for further development (two push incentives and three pull):

- Grants (push)
- Non-Profit Antibiotic Developer (push)
- Diagnosis Confirmation Model (pull)
- Insurance Licenses (pull)
- Market Entry Rewards (pull)

Each of these incentives/models is detailed in this document. Each is meant to stimulate different types of antibiotic innovation as well as different stages of the R&D process (see Diagram 1), addressing the main barriers described previously. They are designed to be complementary. The pull incentives are mutually exclusive, i.e., the same antibiotic cannot be supported simultaneously by more than one pull incentive.

Diagram 1: Antibiotic R&D phases that each incentive/model is anticipated to stimulate



These incentives are a preliminary shortlist. DRIVE-AB is now gathering external feedback and will be simulating the impact of these incentives. Where insufficiencies are found, incentives will be modified or replaced.

DRIVE-AB aims to compose a set of solutions that together comprise a comprehensive reward and support framework that will mobilize the available actors and resources to the greatest extent possible. In addition, the antibiotics reward and support framework should meet the following objectives:

- It should sustainably support innovation (by stimulating both additional public and private financing) to secure the availability of effective antibiotics according to public health needs into the foreseeable future.
- It should reinforce sustainable use of antibiotics in order to conserve the effectiveness of the antibiotics that are in clinical use at any given time.
- It should have integrated provisions for equitable and appropriate patient access, in order to facilitate that all healthcare systems have the ability to ensure that patients receive the appropriate treatment at the right time, and at an appropriate price. Ensuring sustainable use of antibiotics in countries with weak health systems is partly dependent upon price today. Effective mechanisms need to be developed that ensure both access and sustainable use.

Governance and financing:

The five incentives are presented here without discussing potential implementing organizations, governance models or financing mechanisms. Of course, these elements are at the heart of implementing any incentive and need to be presented and discussed in detail. DRIVE-AB is still researching these elements and will present these results at a later stage. There is agreement on the high-level potential implementing organizations and funders (see Table 1).

Table 1: Potential implementing organizations and funders per incentive

Incentive	Implementing organization	Funders
Grants	Multinational body, governments	Governments
Non-Profit Antibiotic Developer	Independent organization	Governments, philanthropic organizations, self-financing
Diagnosis Confirmation Model	Governments, hospital collaborations, hospitals	Governments, private insurers
Insurance Licenses	Multinational body, governments	Governments, private insurers
Market Entry Rewards	Multinational body	Governments

Grants

The incentive:

Grants are non-repayable research funds typically disbursed from public sector or philanthropic entities but may also come from the private sector. Grants are commonly initiated by a call for proposals, whereupon submitted applications become subject to a competitive selection process. Grants are up-front payments and can fully or partially finance the beneficiaries' endeavors. Recipients can be universities, research institutes, and companies (of all sizes). Grants provide non-dilutive capital (i.e., no ownership of results) and can be made conditional to meet specific goals.

Grants should be allocated in a balanced way to optimize the support to drug discovery while boosting more focused research efforts of the laboratories on basic microbiological science. Priority research efforts, as identified in a recent report,¹⁶ include:

- Research on resistant Gram-negative bacteria
- Strengthening chemical libraries tailored for antibiotics discovery
- Research on therapies that are alternatives to antibiotics, such as anti-virulence drugs,
- Collaborative efforts to strengthen communication and sharing of findings between industry and the scientific communities
- Establishment and funding of dedicated centers of excellence in antibiotics research

The type of research and/or development it will stimulate:

Grants aim to increase the publicly available scientific knowledge base in the field, especially basic science and discovery, which in turn increases the flow of ideas and concepts from basic science and discovery onto antibiotic developers. Grants also improve career opportunities for scientists wishing to pursue research in this field, thus expanding the labor pool available also to industry. Some grants, particularly from United States' Biomedical Advanced Research and Development Authority (BARDA) and Europe's Innovative Medicines Initiative (IMI) are also explicitly translational, helping to move targeted compounds through clinical trials. Having more grant funding available for clinical development, especially to SMEs, may further incentivize companies operating in this area, as well as potentially attracting new players who currently see lack of clinical trial funding as a barrier to entry.

Ensuring sustainable use of the resulting antibiotics:

Historically, grants have not been given with any conditions on sustainable use.

Ensuring equitable availability of the resulting antibiotics:

While some grantors like the U.S.' National Institutes of Health (NIH) retain "march-in" rights that are rarely exercised, most grants have not explicitly considered conditions related to equitable access.

Costs and impact:

JPIAMR and EU countries financed € 1.3 billion antibacterial research projects from 2007 to 2013.¹⁷ NIH/NIAID was awarded USD 978 million in "antimicrobial resistance" grants from 2012 to 2014. BARDA has awarded a minimum of USD 175 million and a maximum of USD 600 million to perform

antibiotic clinical trials. The AMR Review has called for USD 2 billion over five years to fund early stage research. The newly created Newton Fund is a result from the UK-China AMR Partnership Initiative aims to attract investments totaling GBP 1 billion. In August 2016, BARDA/NIH will initiate funding of the Combating Antibiotic Resistant Bacteria (CARB) Accelerator, with USD 40 million in year one and a planned USD 250 million over five years. Projects of a similar magnitude are underway in the United Kingdom as well.

These are significant investments, and they fund a variety of research stages from basic science to clinical trials. It is currently unknown how much is dedicated to each R&D phase. The actual impact is difficult to gauge. For example, are the most pressing public health threats being researched? Is there anything that can be done to direct research towards the most pressing health threats without hindering academic ingenuity? A simple analysis of the current antibiotic pipeline presents a mixed result with more activity for non-urgent threat pathogens in clinical trials phases I and II but greater activity for urgent threat pathogens in clinical trials phases III (Table 2). A recent analysis of the eight antibiotics most recently approved by the US' regulatory approval body (FDA) found most were not approved for high priority threats and most of the pivotal trials did not demonstrate clinical superiority against drug-resistant bacteria.¹⁸

Table 2: Pew Trust’s categorization of the existing antibiotic pipeline¹⁴

R&D Phase	Expected activity against a urgent threat pathogen	Number of candidate antibiotics
Phase I	Yes	4
	No	5
Phase II	Yes	6
	No	10
Phase III	Yes	7
	No	3

A clear benefit of grants is that the infrastructure and funding is already in place. Early phase grants also encourage the rebuilding of academic talents, in which the pull mechanisms are dependent upon for new ideas and findings.

Risks and limitations:

Risk / Limitations	Comments
Grants concern activities with highly uncertain outcomes, which imply that there is a certain risk that few clinically relevant compounds will emerge, at least in the short-term.	Funders must be prepared for failures, and to defend such losses to their constituencies. However, grants should be targeted towards science that will help to discover antibiotics for the most pressing public health threats.
Grants can be used at many stages of R&D but should be viewed within the context of the other incentives in order to avoid double financing.	Several of the other incentives mentioned in this document should stimulate traditional private financing such as venture capital and corporate acquisition. It is important to find a careful balance of where grants can facilitate innovation and where private financing sources would otherwise fill a gap given a credible pull mechanism.

Non-Profit Antibiotic Developer

The model:

A Non-Profit Antibiotic Developer is an independent organization that manages and finances a portfolio of antibiotic discovery and development projects through to commercialization. It is not a profit-seeking organization but one that would reinvest any profits back into its development work. However, it may partner with and finance profit-seeking companies to further develop specific antibiotic candidates. It is thereby a Product Development Partnership (PDP), similar to those established for neglected diseases.

PDPs, like Drugs for Neglected Disease *initiative* and The Medicines for Malaria Venture, are non-profit R&D organizations with a focus on developing new medicines, vaccines, or diagnostics for the needs of patients in low and middle income countries. They are often virtual R&D organizations, pursuing portfolio management through investments in R&D projects at universities, research institutes and with the private sector. PDPs are historically grant funded through development aid, and the resulting technologies are priced to ensure accessibility. Its active management of its portfolio differentiates it from organizations that primarily finance antibiotic discovery and development but do not commercialize them, like the United States' Biomedical Advanced Research and Development Authority (BARDA) and Europe's Innovative Medicines Initiative (IMI). (Please see the box above.) The newly launched, Global Antibiotic Research and Development Partnership (GARD), is an example of a Non-Profit Antibiotic Developer.

Comparison of different financing organizations

	Non-Profit Antibiotic Developer	BARDA	IMI
Finances public and private sector R&D	Yes	Yes	Yes
Commercializes antibiotics	Yes	No	No
Patents antibiotics	Occasionally	No	No
Independent organization	Yes	No	No
Stimulates a portfolio of R&D against specific pathogens	Yes	Yes	Broadly
Financing is tied to conditions regarding promoting sustainable use and ensuring equitable availability of the resulting antibiotic	Yes	Not to date	Not to date

The type of research and/or development it will stimulate:

A Non-Profit Antibiotic Developer will focus on areas of research and development that are uninteresting to the private sector, such as innovations not protected by intellectual property and technologies with exceptionally high development risk.

There are several types of desirable antibiotic R&D activities that can be classified as incremental. Typically in these cases patents have expired and, therefore, the additional R&D results are more difficult to protect from competition. For example, screening for optimal combinations of existing, older antibiotics may offer increased efficacy and overcome specific resistance mechanisms. Combination therapy is already widely used, but not systematically and often without an evidence base.¹⁹ Research is needed to find the most effective drug combinations and optimize their use.^{20,21} Another area is reformulations of existing antibiotics, for example modifying an antibiotic to tolerate higher temperatures or to create oral pediatric formulations. Lastly the private sector may have stopped development of an antibiotic candidate years ago and now the patent has expired and the

regulatory exclusivity periods are too short to recoup the development cost. All of these are examples where R&D investments are needed and may be considered “low hanging fruit”.

Other types of desirable antibiotic R&D activities can be classified as those with an exceptionally high development risk. Some new antibacterial products may be considered too risky for a number of reasons, such as no clear regulatory pathway to market. In these cases, the private sector may simply choose not to develop these technologies as all pull incentives are only paid upon successful commercialization. Alternative technologies like utilizing the gut microbiome (i.e., the microorganisms living in the intestines) fall into this category, since treatment may need to be tailored for each person. A Non-Profit Antibiotic Developer can utilize alternative routes to make the knowledge and evidence available. For example, in the case of the gut microbiome, if it is not possible to develop as an antibiotic, it may be possible to develop a standard treatment procedure.

Ensuring sustainable use of the resulting antibiotics:

As a non-profit entity, the developer is not motivated by profits and should act to promote sustainable use. PDPs are well versed in the challenges of healthcare systems in low and middle income countries. They focus on developing products that tolerate high tropical temperatures, are easy to administer and appropriate based upon local resistance patterns (as evidenced through PDP efforts in tuberculosis, malaria and HIV). These efforts help to ensure that patients receive an appropriate dose which promotes the sustainable use of the resulting antibiotics.

Ensuring equitable availability of the resulting antibiotics:

The focus of an antibiotic developer who is not profit-driven is arguably easier to shift towards the achievement of global access-related goals. Indeed, existing PDPs have a core mandate to improve access of life-saving commodities, especially in low and middle income countries.

Costs and impact:

The total funding needs of a new Non-Profit Antibiotic Developer will depend upon the composition of its portfolio. To give some indication of costs, please see Table 3 for examples from the neglected diseases field, as developed by Drugs for Neglected Disease *initiative*.

Table 3: Examples of development costs from the Drugs for Neglected Disease *initiative*²²

Medicine	Disease	Type of Innovation	R&D Phases Included	Cost
Fexinidazole	Sleeping Sickness	A “rediscovered” new chemical entity	Preclinical to commercialization	€ 26.5 million
SCYX-7158 Oxaborole	Sleeping Sickness	New chemical entity	Discovery to commercialization	€ 38.3 million

These examples are the actual costs of the development activities and do not include the cost of failures, i.e., development activities started but stopped due to a scientific failure. For a more complete financing picture, DNDi’s expenses from 2003-2013 were € 182.5 million. In this time period it delivered six improved treatments and developed twelve new chemical entities (initiated at different development phases).²³

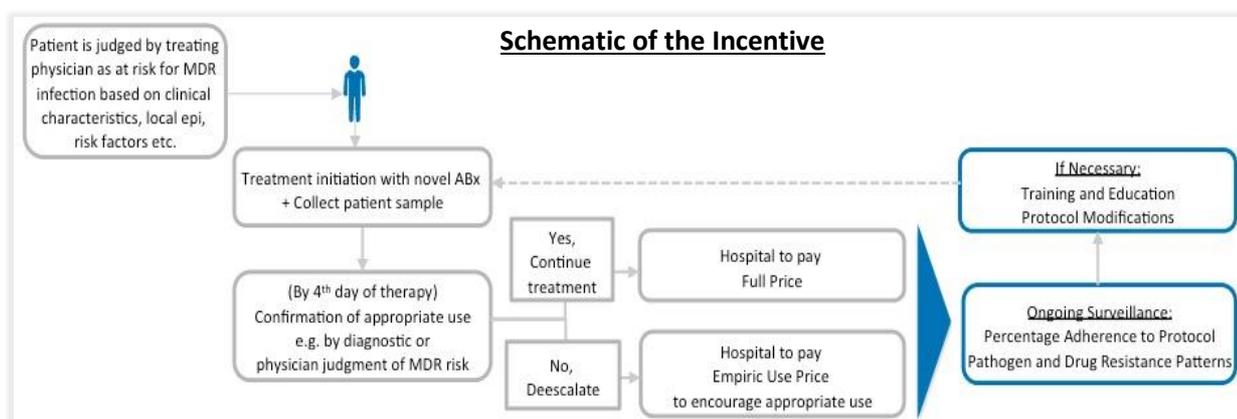
Risks and limitations:

Risk / Limitations	Comments
Agreeing on global priorities may be challenging given that financing countries may also benefit from these innovations.	There needs to be agreement or recognition of global antibiotic development needs, also taking into account the needs of low and middle income countries.
The non-profit antibiotic developer may find it difficult to motivate private actors to participate in its projects, unless sufficiently high payments to these actors are awarded, which would risk quickly depleting its pool of finances.	Companies with several alternatives where to allocate their human resources would be harder to convince and motivate, restricting the interested partners to those who simply have free capacity or at worst may be less equipped to successfully conduct drug development projects. Hence the selection of the right operating partners involved in each project is essential.
PDP financing is relatively stable. Creating a new PDP may cannibalize financing from neglected tropical diseases.	Existing PDPs are grant funded through development aid and philanthropic support. Often their financing is earmarked for specific projects. These funding streams could finance the short-term activities described previously which will directly benefit low income countries. However, there may be concerns that financing an antibiotic-related PDP will further fragment existing PDP financing. Total PDP financing has remained relatively static around USD 500 million per year since 2007, with about half of these funds coming from the Bill and Melinda Gates Foundation. ²⁴

Diagnosis Confirmation Model

The incentive:

The Diagnosis Confirmation Model is a diagnosis-driven, dual-pricing model where a premium price is charged if the antibiotic is used for the entire course (based on a confirmed diagnosis or clinical decision) or a lesser price if the antibiotic is used first empirically and then promptly deescalated after the receipt of the diagnostic/laboratory results. This is not a delinkage model, i.e., revenues are still determined by sales volumes. However, the model addresses the tension between stewardship and volume-based revenue models through targeted modifications to existing reimbursement systems for antibiotics. These adjustments support and reinforce key antimicrobial stewardship components (diagnostics, deescalation, regimen monitoring, and surveillance) while also building on the market-based “pull” mechanism which drive innovation in other therapeutic areas. It is designed for severe infections treated in hospital settings, where novel antibiotics for multidrug resistance (MDR) pathogens are typically used.



The model allows for physician judgment to select, if appropriate, initial (empiric) therapy with a novel antibiotic while awaiting laboratory confirmation of the diagnosis of the specific organism and antibiotic resistance. An empiric therapy approach (e.g. initiation of treatment in the absence of laboratory confirmed data) is needed because severe infections require timely treatment, and laboratory data can take up to several days to be received. Example infections could include, but are not limited to, severe pneumonia and severe bloodstream infections.

After laboratory data are received, the physician is able to determine whether to continue the treatment with the novel antibiotic chosen or to change treatment to an older and less costly antibiotic (i.e. “deescalate treatment”). Based on the decision to continue or discontinue the novel therapy, there would be two levels of reimbursed price:

- **Empiric Use Price:** If the decision is made to deescalate the novel therapy on or before, for example, the 4th day of therapy, the reimbursement price for the first few days use would be set to an “empiric use” price that would be lower than the full price, but higher than other less-expensive – yet still effective – choices (i.e. generically available antibiotics) This strategy aims to discourage excessive use of the novel therapy, encouraging formulary-driven shifts to cheaper, effective drugs.
- **Full Price:** If the novel therapy is continued for 4 or more days, for example, indicating it is deemed necessary for treating the infection based on diagnostic results or physician judgment, a price reflecting the full value of the antibiotic would be used for the full course.

The type of research and/or development it will stimulate:

This incentive will stimulate R&D of novel, broad and narrow-spectrum, hospital-based antibiotics with expected moderate to high sales volume, specifically targeting multi-drug resistant bacteria. Since the volume will be driven by the level of the novel therapy's differentiation from other options (e.g. coverage, efficacy, safety, dosing etc.), industry will be incentivized to pursue R&D that could deliver therapies offering meaningful improvements. This incentive may also increase the overall diversity of new antibiotics.

Ensuring sustainable use of the resulting antibiotics:

From a public health perspective, the Diagnosis Confirmation Model is attractive since it promotes the use of a diagnostic and incentivizes de-escalation of the novel therapy in situations where multi-drug resistant diagnosis is not ultimately confirmed or strongly suspected. The difference between the full price and the empiric use price gives an incentive to deescalate the novel therapy in situations where multi-drug resistant diagnosis is not ultimately confirmed. However, depending upon the empiric price, there may be a strong incentive for hospitals to use the novel antibiotic widely within the first four days adding to selection pressure. To counteract this, the empiric use price would need to be set at suitable level.

Data collected from the model could feed into surveillance programs overseen by hospitals, which would provide a feedback loop, or control mechanism, to maintain the quality of stewardship.

Ensuring equitable availability of the resulting antibiotics:

This incentive has no built-in function to encourage equitable availability and it would be extremely challenging to stipulate it at a global level. It relies upon differential pricing, i.e., setting different prices per country. However, it is unlikely that public sector hospitals in low and middle income countries would have information technology systems sophisticated enough to record the actual durations of use. This is likely to be an obstacle to ensuring global equitable availability and require significant capacity-building. In the least developed countries, the new antibiotics could be made available via access programs to partners who can ensure there are appropriate antimicrobial stewardship mechanisms in place, in line with the WHO Global Action Plan's proposal for a comprehensive program of sanitation, hygiene, vaccination, infection control, education, and stewardship.

Costs and impact:

Potential price ranges per day for the full price would depend significantly on factors including the patient population, multi-drug resistance rate, payer budget impact, healthcare system ability to pay etc. Further analysis is needed to determine price ranges and appropriately account for the value novel antibiotics bring to society.

Substantial changes in local patterns of pathogen incidence and drug-resistance over time would lead to periodic evaluations of price levels to ensure appropriate use is incentivized and a fair-value is provided to the healthcare system and the innovator.

Risks and limitations:

Risk / Limitations	Comments
Local resistance data are required to set pricing fairly and incentivize appropriate use.	<ul style="list-style-type: none"> • Model would be used in systems where infrastructure for surveillance exists and would encourage investment in surveillance and education; this excludes many low and middle income countries. • A third party may be needed to oversee the administration of the contract and adherence to the protocol where epidemiology sharing is considered sensitive.
Unpredictable increases in antibiotic resistance over time could result in a high cost burden to the payer, depending on when and how Empiric Use price is set.	<ul style="list-style-type: none"> • The agreement would need to trigger potential adjustments in price based on change in epidemiology.
Stewardship and quality control infrastructure required to implement the model protocol.	<ul style="list-style-type: none"> • This model would only be applicable in systems where adequate stewardship can be implemented; this excludes many low and middle income countries. • Education can be provided to help implement the protocol and improve quality of care, including quality measures. • Partnerships and capacity-building to support introduction and appropriate use in resource-constrained settings.
Setting the Empiric Use price too low could result in overuse of novel therapies or insufficient incentive to deescalate therapy where possible.	<ul style="list-style-type: none"> • Review of adherence to the protocol can trigger adjustments to price as needed. • If hospital has overly high percentage (threshold to be determined) of use that is not in accordance with protocol, then a portion of the Empiric Use funds paid for this use could be returned to the healthcare system for education and surveillance.
Would require acceptance of high prices by payers for novel MDR therapies.	<ul style="list-style-type: none"> • Agreement by payers on criteria to assess the value of new antibiotics that takes into account resistance situation and MDR coverage.
Model may not be sufficient to incentivize development of novel antibiotics for outpatient and inpatient reserve emergency use.	<ul style="list-style-type: none"> • Complementary incentive models, e.g. an Insurance Model, Market Entry Reward, or Non-Profit Antibiotic Developer would need to promote this type of innovation.
This incentive has no built-in provisions for equitable availability and the technological complexity adds additional obstacles.	<ul style="list-style-type: none"> • Potential solutions to improve equitable availability will need to be assessed and agreed in advance, with participation from low and middle income countries and relevant technical agencies.

Insurance Licenses

The incentive:

An Insurance License is an annual license paid to a manufacturer to have access to a specific antibiotic, up to a specified volume. If the threshold volume limit (sometimes called the “collar”) is exceeded, then the payer would be charged an additional amount (either per treatment or a fixed amount to a higher threshold). In a variation of this model (the Cap and Collar Model), there is an additional threshold (the “cap”) where there is revenue-sharing between the manufacturer and the payer.



Insurance-type models are intended for lower volume, hospital-based antibiotics that are considered essential. However, unlike Market Entry Rewards, there is no predefined list of target organisms, rather only non-binding expressions of interest on behalf of payers. It may be that some countries will never use these antibiotics but they want to have stocks on hand for an emergency situation. When used, the antibiotic is available free-of-charge to the payer, whereas in the Cap and Collar model the per-unit cost of the antibiotic is negotiated. The determination of the license fee would be made based on an assessment of unmet need, efficacy and time to market – with a potentially higher payment for innovative drugs.

Agreement to the terms of either insurance-type model is tied to a number of contract stipulations to promote sustainable use and equitable availability (see below). The license is time-limited, potentially 3-5 years per renewable contract. For antibiotics no longer under patent protection, the license could be secured through a tendering process. In some ways this incentive can be viewed as a stockpiling solution, where the manufacturer guarantees the availability of the stockpile under certain pre-determined conditions.

For example, a country may decide that it is desirable to have an insurance product license for an antibiotic that is particularly effective against infections caused by carbapenemase-producing *Klebsiella pneumoniae*, which rarely occur but may be life-threatening when they do. The country identifies antibiotics (which may or may not be patented) that work well against these infections and then enters into negotiations with the manufacturer(s) which results in an annual fee to one or more manufacturer to ensure sufficient access if needed. This model is already in use for pandemic influenza vaccines where governments pay vaccine manufacturers an annual fee to ensure sufficient and timely access in case of an outbreak.

Examples of some of the stipulations tied to this incentive are:

- The antibiotic must have marketing authorization in a specified geographic area.
- The antibiotic must be listed in the hospital antibiotic guidelines for the specified geographic area.
- The manufacturer must be able to supply a specified amount of the antibiotic within a specified timeframe upon payer request.

The type of research and/or development it will stimulate:

This incentive is anticipated to stimulate the development of antibiotics that are considered currently necessary but rarely needed. However, due to the limited predictability of which antibiotics would be considered “essential” at any one time, this incentive would likely only stimulate late phase clinical trials if a large payer, like the United States public system (Medicare), or multiple large payers, like France, Germany and the UK, adopted this model.

Ensuring sustainable use of the resulting antibiotics:

From a public health perspective, the Insurance License incentive is attractive since it removes all developer incentives to increase revenues by growing volume sales. Tight controls would need to be in place to manage use at a local level, to ensure that the antibiotic is not overused due to a perception by hospitals of low unit price. In order to avoid this, the payer would need to implement a shadow-pricing system where wholesalers and hospitals pay a higher price set to encourage usage in line with national guidelines. The wholesaler/hospital price would then be rebated back to the payer. These higher prices would need to be consistent across common trade regions to discourage arbitrage (i.e., the ability to purchase an antibiotic cheaply and resell it for a profit) through parallel imports.

Examples of other stipulations to promote sustainable use are:

- Restrictions that the antibiotic be made available only for human health.
- Providing the annual consumption figures by country to determine per capita consumption and compare to the prevalence of antibiotic-resistant organisms.
- Implementing a warning system where a sudden significant increase in consumption is reported.
- Agreement by the manufacturer not to promote the antibiotic with the exception of assisting national experts in correctly placing the new antibiotic into national guidelines.

Ensuring equitable availability of the resulting antibiotics:

This incentive has no built-in function to encourage equitable availability on a global level. However, large payers could build a standard provision into each contract to specify access requirements (e.g., differential pricing policy, regulatory filing, WHO Prequalification, etc.) or engage with specific global antibiotic access initiatives. For example, an international body could license the antibiotic on behalf of low and middle income countries that are not in a position to purchase the license on their own. These licenses would need to include provisions promoting sustainable use of the antibiotic(s). The shadow price would be set according to local considerations such as alternative drug price, affordability, price in neighboring countries where arbitrage could be an issue, etc. The body that collects the shadow price/cost could also be the one to have a predominant monitoring/surveillance role. The role of this body needs to be drawn up alongside a full picture of the possible financial flows/loops in order to hedge against potential transparency problems.

Costs and impact:

This incentive stimulates development by providing a predictable return on investment and bringing revenue forward in the product life-cycle. The license amount will vary by antibiotic depending upon the perceived value of having access to the particular antibiotic or portfolio of antibiotics.

Since manufacturers will not promote the eligible antibiotics, this will lower marketing and related costs. However, if this incentive is implemented at a national level, there will be higher transaction costs in regards to contract negotiation and maintenance.

This model might also serve as a useful intermediate step towards delinkage; data from experience with insurance licenses now being negotiated will illuminate additional options going forward.

Risks and limitations:

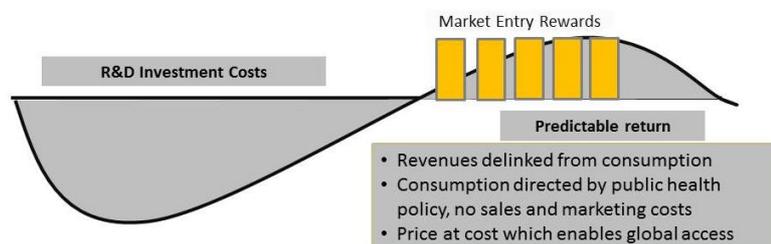
Risk / Limitations	Comments
There is a risk that this incentive can promote arbitrage (i.e., the ability to purchase an antibiotic cheaply and resell it for a profit).	To avoid this risk, wholesalers who sell the antibiotic to hospitals would need to pay the higher hospital price, with this amount rebated back to the payer.
The non-binding list of target organisms implies greater risk to drug developers.	This additional risk makes Insurance Licenses less attractive than Market Entry Rewards for stimulating innovation. Insurance Licenses are likely better at promoting access to critical, low volume antibiotics.
This incentive has no built-in provisions for equitable availability.	Potential solutions to improve equitable availability will need to be assessed along with their potential ramifications on the overall effectiveness of the incentive.

Market Entry Rewards

The incentive:

A global body/coalition of partners guarantees to pay a predefined amount to an innovator that achieves regulatory approval for a new antibiotic meeting specified requirements, including target pathogens. The payment amount

is designed around a base payment with top-up payments for meeting stringent criteria, as proposed by Rex and Outtersen²⁵, see Table 5. Payments are staged, for example, made in the first five years following regulatory approval. By accepting the payment the developer contractually agrees to a set of stipulations regarding global unit prices, global availability, regulatory maintenance, and sustainable use provisions. This is a delinkage incentive, where the reward is not tied to sales volumes. The sum of payments over a fixed time period is estimated to be about USD 1-2.5 billion per high-priority antibiotic (see Table 6) in exchange for an exclusive license, with ‘follow-on’ products rewarded with lower sums.



In exchange for the payment, the manufacturer agrees to:

- Perform regulatory maintenance of the drug, i.e., achieve marketing authorization for the antibiotic in the agreed countries, maintain the registrations and perform pharmacovigilance
- Set agreed global prices if required
- Make annual consumption figures by country publicly available
- Implement sustainable use activities including a warning system where a sudden significant increase in consumption by country is reported to the neutral governing body
- Not to promote the antibiotic in any way, with the exception of assisting national experts in correctly placing the new antibiotic into national guidelines

Table 5: Potential criteria for base payments

Predefined criteria	Payment
Drug approved at a regulatory agency to treat at least one predefined infection caused by at least one or more pathogens listed on a threat assessment list as either <u>urgent</u> , <u>serious</u> , or <u>concerning</u> to public health	One base payment
Has a clinical spectrum of activity on the label that includes one or more <u>urgent</u> pathogens on the threat assessment	Bonus equal to one base payment
Has a clinical spectrum of activity on the label that includes one or more <u>serious</u> pathogens on the threat assessment	Bonus equal to 50% of a base payment
Is the <u>first</u> approved drug to act via a given <u>mechanism of action</u>	Bonus equal to a base payment
Is the second, third, or fourth agent approved to act via a given mechanism of action	Bonus equal to 75% of a base payment for a second agent, 50% for a third agent, or 25% for a fourth agent
Is the fifth or subsequent agent to act via a specific mechanism of action but offers a <u>medically relevant improvement</u> in safety, efficacy, or ease of dosing	Bonus equal to 10% of a base payment

Predefined criteria	Payment
Delivery of agreed pediatric commitment studies	Payments based on model or separate contract open to tender
Is approved for a second, third, or fourth defined infection for a specific agent (requiring additional clinical studies)	Bonus equal to 25% of a base payment
Approved in <u>oral</u> dosage form	Bonus equal to 25% of a base payment

Source: Rex and Outterson with minor modifications²⁵

In a hybrid variation, the global body/consortium would provide a smaller market entry reward to the developer of a new antibiotic once it achieves regulatory approval, and the developer would be allowed to charge higher prices per unit. It is estimated the cost of this model to the global buyer(s) would be GBP 16 billion over 10 years to deliver 15 new antibiotics.²⁶

The type of research and/or development it will stimulate:

Assuming that the Market Entry Rewards are sufficient to generate an internal rate of return to the investor that is more attractive than other commercialization options, this model should have the ability to generate R&D in any area of unmet need as defined by the funders, including R&D activities in low prevalence or emerging bacterial resistant infections (broad and narrow spectrum). However, given the high price tag of this incentive, it is imagined that policymakers would only utilize this incentive for the most pressing public health threats, i.e., high-priority pathogens. This incentive is anticipated to stimulate greater investment in clinical trials from Phase I and beyond and should stimulate traditional financing mechanisms like venture capital.

Ensuring sustainable use of the resulting antibiotics:

From a public health perspective, the Market Entry Reward is attractive since it removes all developer incentives to increase revenues by growing volume sales. Tight controls would need to be in place to manage use at a local level, to ensure that the antibiotic is not overused due to a perception by hospitals of low or no unit price. In order to avoid this, the payer would need to implement a shadow-pricing system where wholesalers and hospitals pay a higher price set to encourage prescribing in line with national guidelines. The difference between the wholesaler/hospital price and the cost price would then be rebated back to the payer. If access considerations lead to different prices globally, arbitrage must be prevented by standard regulatory mechanisms.

The increased transparency surrounding consumption should theoretically also promote sustainable use as national consumption rates can be easily compared and national measures to curb overuse can be expediently addressed.

Ensuring equitable availability of the resulting antibiotics:

The payer would specify the geographical scope and price(s). This could either be limited to funding countries or include wider access. However, the additional costs of wider access (preparation and submission of regulatory dossiers, maintaining of regulatory files, safety monitoring etc.) would then need to be accounted for in the payment amount.

Costs and impact:

Table 6: Estimated Market Entry Reward payments per antibiotic

Source	Payments per antibiotic	Expected NPV benchmark at commencement of R&D
Sharma & Towse ²⁷	USD 2.5 billion (USD 500/year for five years)	USD 300 million
Eastern Research Group ¹³	USD 919 million (spread over entire R&D process and at registration) (US only)	USD 100 million
O'Neill Review on Antimicrobial Resistance ²⁶	USD 0.8-1.3 billion	Not stated
Rex & Outterson ²⁵	USD 200 million base payment for five years (an antibiotic can achieve multiple base payments)	Not stated

The cost of these incentives includes those attributable to attrition during research, development and registration. Since manufacturers will not market the eligible antibiotics, this will lower marketing and other sales-related costs. The output of these incentives highlighted in the above table is one new antibacterial, and is calculated to include the development risk from the pre-clinical stage. It should be noted that the incentive mechanism described above rules out marketing practices and, as such, minimizes post-development and add-on costs, potentially substantially.

Risks and limitations:

Risk / Limitations	Comments
Financing such large amounts will require collaboration and strong financing commitments – potentially a global fund.	<ul style="list-style-type: none"> If financing is not found, private sector investors will continue to exit the market and the remaining investors will move to alternative high price models (which limits access to high-income markets). The incentive requires structures/systems in place to manage and implement the collaboration and financing. It will be difficult to implement this incentive on a country by country basis. It is therefore important to engage with existing multilateral funds (Global Fund to Fight AIDS, TB, Malaria; GAVI) to understand process and lessons learned, and increase advocacy around AMR at G7/G20 and UN.
The incentive may have increased implementation challenges in private systems.	<ul style="list-style-type: none"> There is a need to work with multiple types of payers to ensure the best fit across many countries. This is not a 'one size fits all' model.
No incentive for developer to manufacture the antibiotic after the reward period is complete.	<ul style="list-style-type: none"> There is little interest from generic manufacturers to produce the low volume antibiotic, resulting in an important antibiotic being no longer accessible. To counteract this, countries must tender the purchase of the antibiotic via an Insurance License.
Funding must be secure and prioritization must be consistent over time, given length of clinical	<ul style="list-style-type: none"> Funding commitments must be long-term and cannot be subject to annual budget approvals. There must be broad agreement on the prioritization criteria,

Risk / Limitations	Comments
development programs (8-10 years).	<p>with a very high bar for modifications once it is approved.</p> <ul style="list-style-type: none"> • If manufacturers develop a novel antibiotic that meets the criteria of the Market Entry Reward, the payment would need to be made (even if the targeted pathogen had not emerged).

Table 7: Comparison of DRIVE-AB “Pull” Incentives

Dimension	Diagnosis Confirmation Model	Cap and Collar	Insurance Licenses	Market Entry Rewards (full)	Market Entry Rewards (hybrid)
Delinked model	No	Partially	Yes	Yes	Partially
Reward amount	Negotiable	Negotiable	Negotiable	Predefined	Predefined
Pathogen eligibility requirements	Negotiable	Negotiable	Negotiable	Predefined	Predefined
Stimulates the development of primarily narrow or broad spectrum or pathogen-specific	Broad and narrow	Any	Any	Any	Any
Existing unmet need or emerging unmet need	Existing	Existing	Both	Both	Existing
Market size	Large	Moderate	Low	Low	Moderate
Novel or older antibiotics	Novel	Novel	Both	Novel	Novel
Hospital or community based	Hospital	Both	Hospital	Both	Both
Duration	Short-term, renewable contract	Short-term, renewable contract	Short-term renewable contract	Life of the patent and perhaps beyond	Life of the patent and perhaps beyond
Per unit cost at point of use	Pricing set by manufacturer	Cap and Collar negotiated	No cost up to a specified volume	Cost price	Pricing set by manufacturer
Promotes sustainable use	Moderately	Strongly	Strongly	Strongly	Moderately
Promotes equitable availability	Weakly	Weakly	Weakly	Strongly	Strongly
Implementing organization	Hospitals	Governments	Governments	Multinational body	Multinational body

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