A Critical Assessment of Incentive Strategies for Development of Novel Antibiotics

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EXECUTIVE SUMMARY

In recent years, a concern has emerged in the public health arena regarding the deadly combination of increasing antimicrobial resistance and stunted antibiotic development. Antimicrobial resistance is an evolutionary adaptation that will not cease, but can be mitigated with careful stewardship of existing antibiotics. The decline in investment in antibiotic development is a complex, multifactorial market failure arising from the nature of antibiotic prescribing, current pricing, existing patent structures, and societal expectations.

While combating antimicrobial resistance is the realm of scientists, addressing public health crises due to market failures is the realm of policy makers. This report seeks to provide a basic armamentarium from which to begin that discussion. This project undertook a rapid review of the antibiotic incentive literature using guidelines from the Centre for Reviews and Dissemination. A total of forty-four antibiotic incentive strategies were identified and classified in traditional categories of push, pull, and hybrid mechanisms.

Push methods reduce the cost of researching and developing new drugs. Push incentives are useful because they lower the barriers to entry that preclude small and medium sized pharmaceutical enterprises. In addition, research and development incentives delivered upfront are dramatically more valuable than similar sized future payments, which must be discounted to present value. However, push strategies are troublesome because they can result in conflicting priorities of development trajectory and they expose a funder to the financial risk of project failure.

In contrast, pull mechanisms, which can be categorized as either outcome-based or lego-regulatory, reward successful development of a drug by increasing or ensuring future revenue. These pull methods are beneficial because they only reward successful research, encourage efficient and rapid development, and align the priorities of the developer with those of the funder or regulator. These strategies tend to be problematic because they rely on the payer remaining dedicated to their future payment commitment despite potential changes in funding priorities. It is also a challenge to define the optimal set of drug characteristics linked to the reward so that they are not perversely specific nor too loose resulting in a mismatching of goals.

Finally, a combination of complimentary push and pull strategies can be formulated into a hybrid approach that balances the merits and drawbacks of the individual incentives. A detailed review of the individual advantages and disadvantages of each incentive is provided.

Given the large number of incentives, a framework was developed to assist with the selection of incentives to address two major concerns – market failures and public health goals. Specific objectives within these areas have been identified as:

Objectives to address market failures:

1. Improve the overall net present value for new antibiotic projects
2. Enable greater participation of small and medium sized enterprises
3. Encourage participation by large pharmaceutical companies
4. Facilitate cooperation and synergy across the antibiotic market

Objectives to address public health priorities:

1. Promoting antibiotic stewardship
2. Improving patient access to new antibiotics

To make the selection process manageable, we suggest first selecting a set of incentives that address all four market objectives with the goal of creating an attractive and supportive market for investment in antibiotic research and development. To aid in this task, the incentives are classified into six different types based on their ability to meet these objectives. These incentive types include: broad-spectrum incentives, participation-focused incentives, cooperation and synergy-focused incentives, SME-focused incentives, Big Pharma-focused incentives, and weak market incentives. The broad-spectrum incentives are able to satisfy all market criteria while in other cases a

combination of multiple incentives from different categories could be used. Once this market-centric package has been created, it can be supplemented and reformed to additionally tackle the two major public health objectives: stewardship and access.

There are a number of crucial implementation issues that must be considered prior to finalizing an incentive package. These issues will reflect political priorities, operational realities, and industry demands concerning:

1. The size of the incentives
2. The timing of incentive delivery
3. Governance of the incentive package
4. International coordination
5. Intellectual property laws

The ultimate array of possible incentives to use will be constrained by the outcome of this feasibility analysis. Thus, an effective incentive package will be one that repairs the market failures that have resulted in a dry development pipeline, facilitates public health priorities that reflect the growing need for a sustainable solution to antimicrobial resistance, and function within implementation constraints. Much can be done, but a significant effort will be required to address the impending crisis.

1. INTRODUCTION

Since the discovery of penicillin, infectious microbial organisms have found mechanisms to gain resistance to the existing arsenal of antibiotic drugs. Antibiotics are indispensable in treating serious infections like tuberculosis, meningitis, and pneumonia, preventing post-surgical infections, and managing immunocompromised individuals such as cancer patients.[1,2] It is estimated that antimicrobial resistance (AMR) is directly responsible for 23,000 deaths annually in the US and more than 25,000 in the EU.[3,4] A conservative estimate of the economic cost of bacterial resistance is $20 to 35 billion dollars annually in the US alone.[3] Despite the necessity for new antibiotics, the development pipeline is very limited, especially for drugs that tackle lethal multidrug-resistant Gram-negative bacteria.[5] Pharmaceutical and biotechnology firms are reluctant to develop novel classes of antibiotics because the market is risky and relatively unprofitable. Therefore, innovative solutions are needed to stimulate and foster investment in research and development (R&D) of antibacterial drugs.

The antibiotics market has a number of characteristics that make it financially unattractive. First, antibiotics have higher failure rates in the initial stages of development (Phases I and II of clinical trials) relative to other drug categories.[6] This higher probability of failure is a large financial risk, given that the average cost of successfully marketing a new drug ranges from $800 million to $1.7 billion.[7] Second, the regulatory requirements for market approval in the US and EU have been uncertain and prone to change, creating additional development risk.[8] Third, antibiotics are less profitable than other drug categories: national conservation programs limit sales, antimicrobials become progressively ineffective due to AMR, there is an established generics market with many substitutes, reimbursement systems encourage the use of the cheapest drug, and antibiotics are often prescribed for a brief period.[9,10] Finally, many pharmaceutical companies have reallocated scientific talent and capacity to more profitable opportunities, thereby diminishing what economies of scale they originally possessed.[5,11]

Investment in antibiotics can be incentivized through two broad strategies known as push and pull mechanisms.[11,12] Push methods reduce the cost of researching and developing new drugs. Examples of push incentives include increasing access to research, providing research grants, offering tax incentives, and establishing public-private partnerships for sharing R&D outlays. In contrast, pull mechanisms reward successful development of a drug by increasing or ensuring future revenue. This may be in the form of outcome-based rewards such as monetary prizes, advanced market commitments, and patent buyouts, or as lego-regulatory policies that accelerate the market approval process, extend market exclusivity rights, and increase reimbursement prices. In addition, a combination of complimentary push and pull incentives can be used in a hybrid approach. Proposed hybrid approaches include the Antibiotic Conservation Effectiveness Programme and the Options Market for Antibiotics.

The purpose of this policy report is three fold. First, it will methodically identify and summarize all existing strategies for encouraging R&D of novel antibiotics and classify them using the push-pull framework. Second, it will evaluate the advantages and disadvantages of these strategies. Finally, this report will present a framework for selecting an incentive or combination thereof that addresses market deficiencies as well as other priorities.

2. RESEARCH METHODOLOGY

A rapid review of the literature was performed to identify specific policies, mechanisms, incentives, and business models for stimulating R&D in antibiotics using guidelines from the Centre for Reviews and Dissemination.[13] From this literature search, strategies were identified and classified using the push-pull framework and then their advantages and disadvantages were evaluated. Literature was initially sourced from peer-reviewed journals, augmented with grey literature, and then validated through expert opinion (see Appendix 1 for flow diagram of the systematic search). Going beyond a typical rapid review, a critical analysis of the incentives is conducted using criteria identified in the literature as crucial to designing an effective strategy.

2.1 Identification, screening, & eligibility assessment of peer-reviewed literature

The search protocol for peer-reviewed journals (See Appendix 2 for generalized search strategy) was operationalized through MEDLINE via PubMed, Scopus, Econlit, Business Source Complete, and CINAHL. Zentoc and DARE were also searched; however, no relevant sources were identified in either database. Where possible, search results were filtered to include only literature that focused on humans, published in the last ten years, in English, and either a journal article, review, systematic review, conference report, or interview.

Following compilation of initial search results, the literature was first screened using ineligibility criteria applied to titles and abstracts. Articles were deemed ineligible if they focused on clinical settings, scientific research, prescribing practices, antibiotic stewardship, and any criteria that was refined in the initial search but was not applied to all databases (language, focus on animals, date of publication etc.). The second screening involved reading each article and assessing eligibility. Literature was deemed eligible and relevant to this review if it discussed one or more antibiotic R&D incentive methods.

2.2 Identification of relevant grey literature

Grey literature was screened based on eligibility as it was identified and added directly to the compilation of relevant literature. The literature search began by identifying several key review articles and searching references and citations for articles not already identified. Grey literature was further identified through a Google search for articles, PowerPoint presentations, advocacy statements, and conference listings. Key advocacy groups and policy committees including the Infectious Disease Society of America (IDSA), Action on Antibiotic Resistance (ReACT), the British Society for Antimicrobial Chemotherapy, Knowledge Ecology International (KEI), the World Health Organization (WHO) and the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) were identified and further searched for sponsored literature.

2.3 Analysis

Forty-three unique incentive strategies were identified from reading the relevant works. In this context, strategies is a broad term used to capture single incentives and policies as well as multifaceted business models combining multiple incentives, policies, and conservation mechanisms.

2.4 Expert opinion

This set of forty-three strategies was presented to experts in the field including academics, advocates, industry professionals, and policy makers with the goal of identifying any deficiencies in the results. In total, twenty-six experts were initially approached, nine experts provided feedback, and one new strategy was added to the consolidated list (See Appendix 3 for list of experts that provided feedback).

2.5 Post-review critical analysis

Following compilation of all the incentive strategies, their individual advantages and disadvantages were assessed. Going beyond a basic rapid review, the incentives were then critically analyzed using criteria identified from the literature as important to creating an effective incentive package. These criteria have been used by experts, but have never been jointly used in a single analysis. This critical analysis forms the basis for a framework for selecting an optimal incentive package.

3. RESULTS: IDENTIFICATION & EVALUATION OF INCENTIVES

3.1 Push strategies

Push mechanisms (Box 1) seek to make drug development more attractive by lowering the R&D costs of generating a new drug. These incentives are useful because they reduce the barriers to entry that preclude small and medium sized enterprises (SMEs), which make up a significant portion of the R&D market.[14] These smaller firms frequently lack the capital to translate early pre-clinical research into

clinical development, aptly nicknamed the "valley of death".[8,15-17] Early push funding is advantageous because antibiotics have higher success rates than other drug categories in the final phases of development.[6] In addition, an early-stage R&D push is more valuable than an equal pull incentive, which must be discounted to present value. Spellberg and colleagues found that an early subsidy could be as much as 95% smaller than an equally effective future reward.[18] These policy subsidies can also be linked to discrete R&D stages and drug characteristics to align developer goals with public priorities.[12]

However, there is a significant probability that push incentives will fund projects that fail. DiMasi *et al*. calculated that anti-infective drugs have a 24% chance of making it to market.[6] Therefore, a majority of the R&D risk is borne by the funder. This problem is exacerbated by a principle-agent problem where the developer has asymmetrically more information regarding a project's progress. This permits the developer to act in its own interests. Finally, research subsidies may damage operational efficiency by reducing financial pressure to economize and funder guidance may overly constrain the innovative capability of a developer.[11,12,19]

A practical example of one push mechanism currently in use is the concept of refundable tax credits. This is a corporate tax relief system that can reduce a company's current liability and may be redeemed for cash if this liability is below zero.[19,20] These may be particularly valuable in attracting SME's with potentially lower tax burdens than larger corporations as the refund they receive provides a push mechanism, lowering overall NPV and potentially providing needed capital. In Canada, under the Scientific Research and Experimental Development tax policy, SME"s qualify for a 35% credit, compared to 20% for larger firms.[21,22] There is substantial risk to the government though, in that there are no guarantees the refunded money will go into research or produce the intended target.

Greater control over the direction of research can be attained with a product development partnership. This is a collaboration between public and private entities to facilitate neglected drug development.[11,23] The advantage to this approach is that the sponsor (public entity) can set the research agenda and goals, while spreading the financial risk out over a number of projects.[7] Unfortunately, raising enough capital to fund such projects may be difficult and transparency issues may arise.[23] See Appendix 4 for a summary of the advantages and disadvantages of each push incentive.

Box 1. Push strategies

- *Supporting open access to research* – providing and sharing scientific databases and molecule libraries
- *Grants for scientific personnel* – funding training and development of personnel specializing in R&D of antibiotics
- *Direct funding* – subsidies offered to organizations for the R&D of novel antibiotics
- *Conditional grants* – subsidies offered to organizations for the R&D of novel antibiotics that are specifically tied to conservation conditions in the event the antibiotic is successfully launched
- *Funding translational research* – funding for facilitating cooperation and interaction throughout the entire supply chain including research, commercial development, and clinical application
- *Tax incentives* - tax credits, allowances, or deferrals that are tied to early R&D and reduce a developer's current tax liability
- *Refundable tax credits* – tax credits that can be redeemed for cash instead of reducing current tax liability
- *Product development partnerships (PDPs)* – collaborative agreements to share development risk and reward between a public (or quasi-public) organization and one or more developers

3.2 Pull strategies

Outcome-based pull strategies

Outcome-based pull incentives (Box 2) raise the NPV project valuation by increasing future revenue through monetary rewards determined extraneous to the market. In contrast to push mechanisms, outcome-based pull incentives only compensate successful development, which removes all financial risk from the funder. Furthermore, given that R&D risk is borne by the developer, there is motivation for firms to operate efficiently and launch a drug that meets the efficacy requirements set by the funder.[12,24]

However, financial risk and uncertainty are substantial deterrents for many potential market participants. This applies to SMEs, which often do not have the resources and momentum to move from early stage research to late-stage clinical trials and market authorization. It is also difficult to determine an appropriate magnitude for the prize. A good outcome-based pull mechanism must adequately motivate developers to undertake the R&D risk, but also ensure that the payment is cost-effective from the public perspective. In addition, it is a challenge to define the optimal set of drug characteristics linked to the reward so that they are neither perversely specific nor too general, resulting in a mismatch of goals.[11] Finally, an effective outcome-based pull system relies on a government that is willing to stand by long-term guarantees.

One of the simplest pull mechanisms is a lump sum monetary prize, given for achievement of a pre-determined goal (i.e. drug development). The advantage of such payments is their simplicity, little additional infrastructure or legislative action is needed, and they may be offered by charities as well as governments.[25] However, the success and cost effectiveness of such a prize relies on the determination of its size. Excessively large prizes are wasteful while small prizes do little to stimulate participation.

In contrast, advanced market commitments (AMCs) promise a market to developers, not a lump sum. Qualifying medicine would be guaranteed a product market of $3 billion – this would be accomplished by adjusting price based on the volume anticipated to be sold.[26] The AMC could be designed in such a way to allow multiple winners and encourage follow-on drug development. However, this mechanism does nothing to delink profits from price and volume sold, and the technical specification of what constitutes a qualifying drug may prove difficult. See Appendix 4 for a summary of the advantages and disadvantages of each outcome-based pull incentive.

Box 2. Outcome-based pull strategies

- *Lump sum monetary prize* – a large financial reward for the successful development of a novel antibiotic
- *Milestone monetary prizes* – incremental monetary rewards paid at various stages of the development process
- *Pay-for-performance (P4P)* – developers receive rewards for achieving quality goals relating to the antibiotic's consumption and resistance levels
- *Patent buyout* – large end prize given in exchange for the intellectual property rights to a successfully developed antibiotic
- *Optional reward* – the developer can choose between a patent buyout reward or maintaining the patent for that antibiotic
- *Payer license* – developer sells an annual license for unlimited access to an antibiotic at marginal cost
- *Research tournament* – competitive milestone prizes awarded to the first developer(s) to reach certain checkpoints
- *Advanced market commitment (AMC)* – an agreement to purchase a set volume of antibiotic for a pre-specified price upon successful development
- *Antibiotic Health Impact Fund (AHIF)* – antibiotics registered in the AHIF would receive annual retrospective payments proportional to their share of health impact across the fund's registered drugs
- *Antibiotic Innovation Funding Mechanism (AIFM)* – a combination of monetary payments for licensing patents and a demand-side user fee to fund the prizes
- *Strategic Antibiotic Reserve (SAR)* – a single or group of governments buy or license the patent for an important first-in-class antibiotic to keep the drug from being marketed

Lego-regulatory pull strategies

Lego-regulatory pull incentives (Box 3) offer firms higher market returns for successfully launched antibiotics. Similar to outcome-based mechanisms, lego-regulatory strategies reward only successful research and thereby maximize R&D efficiency and motivation. In addition, by basing the incentive on market factors such as price and market exclusivity, lego-regulatory mechanisms circumvent the issue of determining an appropriate reward.[11]

However, similar to outcome-based mechanisms, the entire R&D risk and financial cost is placed on the developer, thus excluding those firms that do not have substantial capital. Furthermore, many lego-regulatory mechanisms involve market exclusivity extensions that may dampen competition and innovation. There is an incentive for firms to exploit their market exclusivity and delay development of new antibiotics. Generic drugs, which improve drug accessibility through lower prices, are also prevented from entering the market earlier when patents are extended.[11]

One method of rewarding successful research is the use of accelerated assessment, a process by which regular agencies speed up the review process, and is currently available through the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA).[27,28] This has the twin advantages of potentially lowering the cost of development as well as speeding up access to antibiotics by getting them to market sooner.[29,30] The obvious caveat to this is that anything, which speeds up a review designed to ensure safety, will be subject to potential criticism that it may also compromise the safety and efficacy of the process.[29,31]

Priority review vouchers take advantage of the potential value of an accelerated assessment and use this as a reward to give to companies working on neglected pharmaceuticals. Currently this is only available in the US, although this has been proposed in the EU.[32] The real benefit to these vouchers for smaller companies is the ability to auction them off to larger firms, generating a potentially significant cash reward.[11] Unfortunately, this flexibility also creates competition uncertainty, which may lead to firms pulling out if the market is seen as too risky.[7,33] See Appendix 4 for a summary of the advantages and disadvantages of each lego-regulatory pull incentive.

Box 3. Lego-regulatory pull strategies

- *Accelerated assessment and approval* – fast track programs and priority reviews that reduce the length of drug registration and market approval for antibiotics that meet certain specifications
- *Market exclusivity extensions* – increase the period of intellectual property (IP) and data exclusivity offered for an antibiotic
- *Wild card extensions/ transferable intellectual property rights (TIPR)* – extended IP protection that can be transferred to other drugs in a portfolio
- *Conservation-based market exclusivity* – market exclusivity of an antibiotic is tied to meeting effectiveness targets
- *Liability limitations* – legal protection against litigation in the event of injury or death related to antibiotics targeting bioterrorism and pandemic diseases
- *Anti-trust waivers* – relaxing anti-trust laws to allow developers to collude in order to prevent further resistance arising; alternatively, may allow developers to sell on-patent IP to other developers that result in a monopoly over a group of similar antibiotics
- *Sui generis rights* – offers market exclusivity to a firm for IP that has come off patent
- *Value-based reimbursement* – Setting reimbursement prices for antibiotics based on health technology assessment of the drug's value to society
- *The Generating Antibiotics Incentives Now (GAIN) Act* – a US bill ratified in 2012, which provides additional market exclusivity, priority review and fast track approval, and Food and Drug Administration guidance for antibiotic development
- *Limited Population Antibacterial Drug (LPAD) approval* – a streamlined clinical trial process for novel antibiotics that allows the drug's safety and efficacy to be studied based on substantially smaller, faster, and less expensive trials
- *Priority review vouchers (PRVs)* – vouchers for accelerated regulatory review awarded post-approval to developers of an antibiotic and can be sold or transferred to other products within the developers portfolio
- *New technology add-on payment (NTAP)* – a US hospital reimbursement plan that pays over and above the diagnostic related group category for a particular treatment
- *Developing an Innovative Strategy for Antimicrobial Resistant Microbes (DISARM) Act* – a proposed US bill that would build on NTAP by offering permanently higher payments for qualified antibiotics to those hospitals participating in the Antimicrobial Use and Resistance Module of the CDC's National Healthcare Safety Network

3.3 Hybrid strategies

Each push, outcome-based pull, and lego-regulatory pull mechanism has distinct advantages and disadvantages and it is clear that a single approach is not an adequate solution.[11] Therefore, a combination of the above incentives or a hybrid strategy (Box 4) that balances the varying attributes of the mechanisms may be needed.

An example of a hybrid model is the Antibiotics as Public Goods Model, which combines an open-source discovery platform, milestone prizes, PDPs, and patent buyouts.[34] This mechanism is unique because it prioritizes early research of natural molecules, which are the basis for over 75% of antibiotics reaching the market.[35] At the core of this model is an open-source platform that fosters an international research community that pools human, technical, and material resources. This strategy is particularly beneficial to SMEs because milestone prizes and funding through PDPs help them overcome early-stage development barriers. Furthermore, patent buyouts serve to add promising intellectual property to the research commons. These public patents can be licensed out to generic firms, which can price close to marginal cost in the poorest countries. Moreover, by decoupling sales volume from revenue, firms are no longer incentivized to over-market their drug.[34] But, this proposal is problematic for several reasons. First, given the early-stage focus of this model, the funder is exposed to high risk that the purchased IP or cash injection does not contribute to any meaningful development. Second, it is technically challenging to calculate a patent buyout price that is both social optimal and large enough to entice developers.[11] Third, it may be difficult to stimulate successive innovation on publicly owned intellectual property. Finally, it is a significant implementation hurdle to establish a new international entity that will govern acquired IP, operate the discovery platform, and manage the prize fund.

A very different hybrid strategy is the US-centric Rewarding Antibiotic Development and Responsible Stewardship (RADARS) Program.[36] The RADARS Program is comprised of a NTAP-like hospital reimbursement scheme and a five-year minimum revenue guarantee for developers of novel antibiotics. Since it is designed to complement the LPAD approval system, Qualified Infectious Disease Products (QIDP) designation, and GAIN Act, this incentive package integrates itself well into the US health system. The RADARS Program particularly incentivizes major pharmaceutical companies because it reduces reimbursement risk and does not interfere with established patent culture. The minimum revenue guarantee is conditional on the developer not promoting the sale of the antibiotic through its marketing force. Therefore, if the minimum guarantee is set high enough, there is no incentive for the developer to over-market the new antibiotic.[10] For the most part, the Program's disadvantages are related to the hospital reimbursement payments. The higher reimbursement rates allow developers to charge higher prices, remove the financial incentive for hospitals to limit inappropriate prescribing, and place the funder at risk of overpaying for antibiotics that become sub-optimal in the future.[10] Lastly, the US focus of the program prevents the model from being directly applied in other settings. See Appendix 4 for a summary of the advantages and disadvantages of each hybrid incentive.

Box 4. Hybrid strategies

- *Special drug designation status* – in similar fashion to the current EU/US orphan drug designation, novel antibiotics are given market exclusivity over the indication, additional data exclusivity, grants for clinical research, tax credits on clinical costs, protocol assistance, and accelerated review
- *Options market for antibiotics (OMA)* – a funder pays a developer a premium in return for the right to purchase a set volume of antibiotics at a discount upon successful launch
- *Office of Health Economics (OHE) model* – combines an AMC at a national or supranational level and local value-based pricing
- *Antibiotic Conservation Effectiveness (ACE) Programme* – a comprehensive system involving value-based reimbursement, P4P payments, conservation-based market exclusivity, and anti-trust waivers
- *Project BioShield Act* – a US bill enacted in 2004 that provides a guaranteed federal market (i.e. an AMC) for medical countermeasures to treat chemical, biological, radiological, or nuclear threats as well as a federal funding system to stimulate development of drugs not ready for procurement
- *Rewarding Antibiotic Development and Responsible Stewardship (RADARS) Program* – combination of NTAP payments for novel antibiotics and a guaranteed minimum annual revenue for developers over the drug's first five years on the market

- *Antibiotics as Public Goods* – milestone monetary prizes for early stage antibiotic developments, non-exclusive licensing for promising antibiotics, and an open source platform to share intellectual property, data, clinical results etc.
- *LPAD Plus* – the LPAD approval system combined with a monetary prize in return for conservation commitments and marginal cost pricing
- *WHO Global Consortium* – a multifaceted model combining milestone prizes and research grants for promising drug candidates, open source sharing of knowledge and information, publicly financed clinical trials, patent buyouts of successfully developed antibiotics, and advanced purchase commitments for generic distribution
- *GlaxoSmithKline (GSK) Delinkage Model* – an annual payer license combined with a variety of pull incentives such as PDPs, tax credits, and research grants

3.4 Mechanisms to fund incentives

Some proposed strategies focus on how to fund the incentives discussed above (Box 5). These mechanisms are not incentives themselves, but could be used to augment an incentive package and relieve some of the financial burden inherent in incentivizing R&D of antibiotics. For instance, the Antimicrobial Innovation and Conservation (AIC) fee consists of a flat rate charged on the wholesale purchase of an antibiotic. It acts as a Pigouvian tax that internalizes the costs, or negative externalities, of growing AMR from overuse of antibiotics. The advantages of the AIC fee are that it induces demand-side conservation of antibiotics through higher prices, sustains antibiotic R&D funding programs, and can be adjusted to reflect an antibiotic's therapeutic value and risk of furthering AMR.[37] However, the AIC fee does not incentivize pharmaceutical firms to develop novel antibiotics.[29] Also, the higher prices afforded by the fee may hinder patient access and prevent effective use of antibiotics.[38] See Appendix 4 for a summary of the advantages and disadvantages of each funding mechanism.

Box 5. Mechanisms to fund incentives

- *Fast-track option (FTO) for funding* – auction priority review vouchers (PRVs) to developers and use the earnings as push funding for antibiotic R&D
- *Antibiotic Innovation and Conservation (AIC) fee* – a tax applied per prescription used to fund push incentives and stewardship programs

4. DISCUSSION: A FRAMEWORK FOR SELECTION OF INCENTIVES

4.1 Creating an attractive & supportive environment for investment

This review has shown that there is a plethora of potential incentive strategies, each with their own merits, drawbacks, and level of complexity. Therefore, a framework is needed to select a comprehensive and effective incentive package. Given the serious market failures outlined earlier, the key goal of an antibiotics incentive package must be to create an attractive and supportive environment for investment. To achieve this, the following objectives must be met:

1. Improve the overall net present value (NPV) for new antibiotic projects
2. Enable greater participation of SMEs
3. Encourage participation by large pharmaceutical companies
4. Facilitate cooperation and synergy across the antibiotic market

Improve the overall NPV for new antibiotic projects

Net present value is the sum of all costs and revenues of a given project adjusted for the time value of money and risk of failure. It is a general measure of the profitability of a project. Sharma and Towse estimated the current risk adjusted NPV for developing an antibiotic to be -$50 million. In contrast, the risk adjusted NPV for a musculoskeletal drug is +$1.15 billion and for a neurological drug is +$720 million.[7] As long as the NPV for antibiotic projects remains negative or relatively low, any company looking to maximize profits will not spend significant resources on this class of drugs. Financial incentives that increase revenues, decrease costs, or lower the risk of R&D make investment more

appealing to all market players. Sharma and Towse suggest that a reasonable target NPV should be $200 million, which would make investment in antibiotics competitive with most therapeutic classes.[7]

Enable greater participation of SMEs

Small biotech corporations and spinoffs from university research labs hold promising, novel ideas and actually make up a majority of pharmaceutical R&D market share. Munos found that, between the early 1980s to early 2000s, the proportion of new drugs attributable to SMEs had increased from 23% to 70%.[14] However, SMEs have much smaller capital reserves than large pharmaceutical companies, hindering the transition from initial research to expensive trials required for market approval. Mossialos *et al.* argue that this is the key barrier to preventing many SMEs from participating in antibiotic R&D.[11] Once past the initial research and early clinical trials, the risk of antibiotic projects drops.[6] Incentives that provide milestone payments, early seed money, or reduce the cost of initial R&D are central to levelling the market playing field.

Encourage participation by large pharmaceutical companies

Large pharmaceutical companies (Big Pharma) do not have the same capital restrictions faced by most SMEs. If a project is determined to be significantly profitable, then large pharmaceutical firms can secure the needed funding. However, they are more concerned with the antibiotic market's uncertainty with regards to size, risk, volatility, and regulation. Big Pharma companies need annual revenues of approximately $800 million for a drug to remain profitable. In contrast, SMEs often only need to generate revenues of $100 to $200 million per year.[12] For this reason, large companies are looking for greater revenue certainty and regulatory transparency. These come from credible market commitments and policies awarded by the government as well as large financial rewards for successful antibiotic development.

Facilitate cooperation and synergy across the antibiotic market

There is an opportunity to encourage cooperation and synergy among key industry, academic, and government players in the antibiotic market. This involves sharing information, resources, and expertise among stakeholders to create additional value in the market. Incentives that facilitate this, reward collaboration, allow firms to cooperate to meet public health goals, provide important human resources, streamline the supply chain, and improve regulatory transparency. Not only do these incentives indirectly reduce the cost of antibiotic R&D, but they also help align public and private priorities.

A market-based framework for incentive selection

The primary goal of an incentive package is to create an attractive and supportive market for investment in antibiotics. As discussed above, this is accomplished by improving the NPV of antibiotic R&D projects, enabling SMEs to participate in the market, encouraging Big Pharma companies to participate in the market, and facilitating cooperation and synergy among all stakeholders. Therefore, the following framework has been developed to identify which incentive, or combination of incentives, can best meet these criteria. (See Appendix 5 for assessment of incentives across the market criteria). As seen in Table 2, each incentive has been classified into one of six types, depending on its ability to meet the market criteria.

Table 1. Classification of Incentives

	Incentive Type	Definition
1	Broad spectrum market incentives	Meet all four market criteria
2	Participation-focused incentives	Improve NPV and entice both SMEs and Big Pharma to invest in antibiotic R&D, but may not facilitate cooperation and synergy
3	Collaboration & synergy-focused incentives	Facilitate cooperation and synergy
4	SME-focused incentives	Improve NPV and primarily benefit just SMEs, but may not facilitate cooperation and synergy

5	Big Pharma-focused incentives	Improve NPV and primarily benefit just Big Pharma, but may not facilitate cooperation and synergy
6	Weak market incentives	Incentives or funding mechanisms that only meet one of the four market criteria

It then follows that an incentive package that aims to create a supportive and attractive market for investment in antibiotics could be created through:

1. A single Type 1 incentive,
2. A combination of Type 2 and Type 3 incentives
3. A combination of Type 3, Type 4, and Type 5 incentives

Type 6 incentives could be used, but tend to be weaker market incentives and may be less effective at generating investment and market interest.

Table 2. Market-based Framework for Selection of Incentives

Type 1: Broad Spectrum Incentives	
• PDP (Ps) • Special drug designation (H)	• Antibiotics as public goods (H) • WHO global consortium (H)
Type 2: Participation-Focused Incentives	
• Refundable tax credit (Ps) • Milestone prizes (Pl) • AIFM (Pl)	• OMA (H) • Project BioShield (H) • GSK Delinkage (H)
Type 3: Cooperation/Synergy-Focused Incentives	
• Supporting open access (Ps) • Funding translational research (Ps) • AHIF (Pl) • LPAD (LR)	• Anti-trust waivers (LR) • RADARS Program (H) • LPAD Plus (H)
Type 4: SME-Focused Incentives	
• Grants for scientific personnel (Ps) • Direct funding (Ps) • Conditional grants (Ps)	• Patent buyout (Pl) • Optional reward (Pl) • SAR (Pl)
Type 5: Big Pharma-Focused Incentives	
• Tax incentives (Ps) • End prize (Pl) • Payer license (Pl) • AMC (Pl) • Accelerated assessment & approval (LR) • Market exclusivity extensions (LR) • Conservation based market exclusivity (LR) • TIPR (LR) • Liability protection (LR)	• Sui generis rights (LR) • Value based reimbursement (LR) • GAIN Act (LR) • PRV (LR) • NTAP (LR) • DISARM (LR) • OHE Model (H) • ACE Programme (H)
Type 6: Weak Market Incentives	
• P4P (Pl) • Research tournament (Pl)	• FTO Funding (F) • AIC Fee (F)
Legend: **Ps** – Push incentive **Pl** – Pull incentive **H** – Hybrid push-pull incentive **LR** – Lego-regulatory incentive **F** – Incentive funding mechanism	

4.2 Factoring in public health objectives: stewardship & access

However, beyond creating a viable market for antibiotics, there are two key public health objectives that must be considered. These include:

1. Promoting antibiotic stewardship
2. Improving patient access to new antibiotics

Promoting antibiotic stewardship

Research and development of antibiotics also needs to be sustainable, not just profitable. The traditional patent-based business model rewards developers through market exclusivity, which provides the opportunity to price high and drive sales. Once a patent expires, the market is flooded with generic drugs that compete based on sales volume in a race against impending resistance.[10] This unsustainable business model reinforces the over-marketing and over-consumption of antibiotics that has contributed to high levels of resistance. Simply increasing developer return on investment (ROI) does not address this problem directly. Numerous experts have proposed antibiotic business models that reinforce conservation efforts by completely severing a developer's ROI from sales volume and price.[10-12,39,40] This concept is known as 'delinkage' and is beneficial for three key reasons. First, it provides developers with a concrete ROI that is extraneous to the market. Second, delinkage removes the motivation for developers to over-market their antibiotic. Third, it facilitates access to new antibiotics for those who need them most.[10] Other experts advocate the use of demand-side antibiotic usage fees to internalize the negative externalities accompanying antibiotic use.[37,41] This fee can then be used to finance other incentive mechanisms such as milestone payments or end prizes.

Improving patient access to new antibiotics

It is generally agreed that patients should have access to new antibiotics when they have a legitimate need for them. However, under the current patent-based business model, developers are incentivized to distribute their new antibiotics based on ability to pay instead of need.[10] This may not be a problem for countries with public coverage, but, in countries that rely on private health care such as the United States or developing countries, drug prices remain a significant hurdle to patient access. This issue can be complicated by conservation related restrictions on antibiotic use as well as technical challenges with distribution. Multiple proposed incentives try to overcome this issue by transferring or licensing out a new antibiotic's patent to the government along with the responsibility of distribution and equitable access. Other proposals streamline the regulatory approval process to allow new antibiotics with significant therapeutic value to reach the market faster.

Factoring in public health objectives

Selection of incentives using the above market framework must be done with consideration of public health goals. An incentive package that meets the four market criteria may not effectively support these public health goals. For instance, the Type 1 Incentive, special drug designation, has minimal influence in ensuring antibiotics are appropriately used (See Appendix 5 for assessment of incentives across the public health criteria). In this case, an additional incentive or incentives are necessary to augment this package. Aspects of conservation could be promoted through conditional grants and P4P prizes alongside the special drug designation incentives that stimulate market investment. In some cases, incentives may directly contravene public health objectives. For example, market exclusivity extensions and value based pricing directly incentivize firms to continue over marketing antibiotics and distributing based on ability to pay. For this reason, these types of incentives may need to be altered or not included in the package. Market exclusivity extensions could be swapped out for conservation-based market exclusivity extensions and value based pricing could require continual reassessment to reflect antibiotic effectiveness.

4.3 Factoring in implementation feasibility

Not only does any potential incentive package need to be comprehensive, it must also be feasible. Many of the proposals discussed herein have been developed on a theoretical level, but rarely tested or deployed. While design of appropriate incentives is challenging, it pales in comparison to the

political, regulatory, industry, and financial hurdles that may be faced during implementation. A comprehensive strategy that is unwieldy, too complex, and financially exorbitant provides no advantage (See Appendix 5 for general assessment of implementation feasibility of the incentives). Therefore, more pragmatic design constraints must be considered. These will ultimately reflect a nation's political priorities, operational realities, and industry demands concerning:

1. The size of the incentives
2. The timing of incentive delivery
3. Governance of the incentive package
4. International coordination
5. Intellectual property rights

There are obvious financial constraints on the size of the incentive, as well as differing philosophies on the role of direct government involvement. A related challenge concerns managing the selected incentive package. A new organization setting may be required to determine public health priorities, define the optimal number and depth of drug specifications linked to incentives, to calculate socially fair rewards, and to monitor development progress. This is especially important as many of the recent proposals operate on a global scale (e.g. AHIF, AIFM, WHO Global Consortium) and require coordination, input, and agreement across borders. This new organization could operate under a new agency or as part of an existing forum such as the G-20.

One of the potentially biggest hurdles to implementation for some incentives is the assignment or transfer of intellectual property. From a public health perspective it makes sense to shift control of new antibiotic IP from the private to public domain, but this change poses a risk to the industry. Many pharmaceutical companies want to keep patent rights because it provides additional assurance that costs can be recouped if incentives and policies are reneged or are inadequate. Most delinkage models are based on the concept of transferring IP to the public domain (e.g. AHIF, SAR, Project BioShield); therefore, if this is not a feasible option, these models become irrelevant. However, if this were the case, delinkage can still be created through incentives such as payer licenses, guaranteed revenue minimums (e.g. RADARS), or AMCs.

4.4 Example applications of the framework

Given the market failures that inhibit antibiotic R&D, we suggest beginning with designing an incentive package that first addresses market deficiencies. The framework outlined above is a useful for this purpose. This package can then be augmented and altered to additionally tackle public health issues regarding antibiotic conservation and patient access to new antibiotics. However, incentive selection will be largely determined by operational realities. Therefore, it is important to be aware of underlying political and industry priorities that may create barriers to implementing a certain incentive package. The following are three examples of the application of the above framework in devising an appropriate incentive strategy. The most effective combination of incentives will likely be unique to each country. Therefore, the following examples should be taken as illustrations, not recommendations.

Scenario 1: A single Type 1 Incentive

The WHO is currently developing a Global Action Plan for antimicrobial resistance. As part of this initiative, on May 13, 2014, the WHO hosted a "Technical Consultation on Innovative Models for New Antibiotics' Development and Preservation." The meeting was concluded with the WHO's current model for generating antibiotic innovation.[42,43] This well rounded, hybrid model has five parts: (1) support at the drug discovery stage through milestone prizes and an open source platform, (2) grants for academics, SMEs, and big pharmaceutical firms to lower development barriers and risk, (3) patent buyout end prizes for proven novel antibiotics, (4) public funding of clinical trials, and (5) advance purchase commitments used to preserve antibiotics.[42] The WHO's model attempts to create a PDP across the entire pharmaceutical value chain, or what is referred to as a global consortium. The WHO global consortium explicitly addresses each of the six objectives. Early milestone payments enhance project NPV by reducing early costs, which can have an even greater impact overall due to the time value of money. SME participation is explicitly encouraged with early stage grants and an open source platform. Public funding of clinical trials appeals to large and small firms alike by reducing overall project costs and risk.[44] Patent buyouts facilitate antibiotic stewardship by allowing the

producer to avoid excessive marketing or production. However, to be attractive, these end prizes would need to be sufficiently large, and calculating this in such a way to minimize waste while providing sufficient incentive may prove difficult. Patient access could be assured by partnering with worldwide generic producers who could keep costs low for patients.[10] Still, the consortium itself, along with its financing for public trials and end prizes, would have to be publicly financed, shifting costs and risk to the public sector. Given the massive scope of this model, there are numerous implementation issues that pose serious challenges to overcome. These include attaining adequate public funding for grants, patent buyouts, and clinical trials, coordinating a new global entity to manage the consortium, and liaising with industry to reach an agreement on IP rights.[10]

Scenario 2: A combination of a Type 2 and Type 3 incentive

The Options Market for Antibiotics (OMA) model is a hybrid mechanism that allows government or NGO purchasers to invest in a drug in early stage development. In this model, funders may purchase the right to buy a specified number of antibiotics at a reduced price, if and when the antibiotic ever made it to market.[45] In many ways, this could be considered a form of milestone payments, but with a future discount for options holders. The early payments, if large enough, could both improve the overall NPV, as well as enable greater participation of SMEs. Larger pharmaceutical firms may be attracted by the risk-sharing element of the venture, in that funders may pay when antibiotics are in early clinical development. This also indirectly signals a potential commitment to purchase the product upon marketing approval. Lower prices, or even marginal cost pricing, at marketing approval will help to facilitate patient access. In addition, antibiotic stewardship can be promoted by combining the OMA with an AMC. Bulk purchasing commitments would shift control of sales volume to the sponsor and allow for appropriate distribution of the antibiotic. However, such a scheme would do little to directly facilitate cooperation among corporations, unless it was combined with modifications to anti-trust laws. If enacted in isolation, anti-trust waivers could hinder patient access to medicine by allowing collusion among producers to maintain artificially high prices. The goal of such reforms would be to promote cooperation and synergy across the antibiotic market.[11] While cooperation would be desirable in the early development phases, it would not be desirable in the marketing phase with regards to setting prices. Such reforms could be applied to the OMA model by allowing companies to share early stage data, potentially increasing the transitional probabilities from one phase to the next in later development.

Scenario 3: A combination of Type 3, Type 4 and Type 5 incentives

The Antibiotic Conservation and Effectiveness (ACE) Programme is a hybrid strategy that combines outcome-based and lego-regulatory pull mechanisms with the objective of promoting antibiotic conservation. The Programme has four key components: (1) P4P payments centred on public health and conservation goals, (2) conservation-based market exclusivity, (3) value-based reimbursement that ties drug pricing to the effectiveness of the drug, and (4) anti-trust waivers that allow coordination of conservation activities between developers.[40] Given the pull-centric nature of the ACE Programme, this incentive package particularly targets Big Pharma. Therefore, it would be beneficial to augment this package with a SME-focused incentive such as direct funding. Antibiotic research addressing specific health priorities can be targeted through direct funding and can include expert technical and managerial help that may prove useful to SMEs with less experience. The ACE Programme does not facilitate patient access nor promote cooperation and synergy between industry and the government. Thus, there is role for a Limited Population Antibacterial Drug (LPAD) approval system in this incentive package. Under, the LPAD approval system, the safety and efficacy of an antibiotic targeting a newly resistant pathogen would be examined through smaller, faster, and less costly clinical trials. LPAD designated antibiotics would be limited to a narrow indication for which there is a particularly high patient need and therapeutic benefit. With this system the regulatory agency would provide significant guidance to the developer and continue monitoring the effectiveness of the drug beyond approval.[46]

4.5 Final thoughts

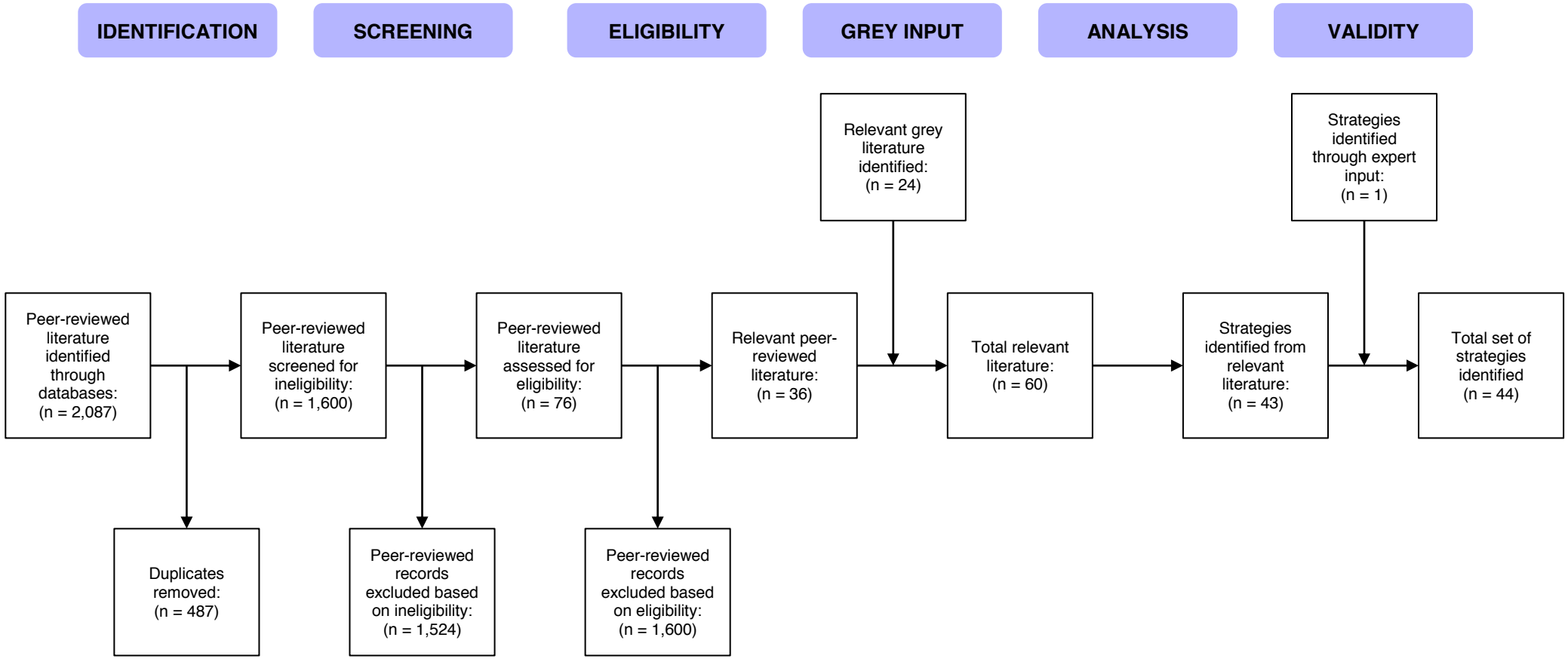
In transitioning from single incentives to more complex, international business models, the implementation becomes significantly more difficult. From our perspective, a feasible, yet comprehensive, incentive strategy likely will include a wide selection of smaller incentives as opposed to a revolutionary antibiotic business model. Our ideal package would include several incentives that

facilitate cooperation and synergy throughout the market, one or two R&D-linked push incentives, and a large pull incentive rewarding successful development.

5. CONCLUSION

Antimicrobial resistance is a complex and immediate health policy problem. There are multiple market failures that make it financially unattractive for pharmaceutical and biotechnology companies to invest in antibiotic R&D. This problem is complicated by the perverse market incentives to oversell antibiotics and distribute based on ability to pay instead of need. Due to the severity of the problem, many solutions have been recently proposed. This rapid review has identified forty-four incentives that could be used to encourage and accelerate R&D of novel antibiotics. These incentives have been classified using the push-pull framework and their individual advantages and disadvantages have been evaluated. However, given the large number of possible incentive schemes, a framework is needed to select an effective package of incentives. An ideal solution will tackle the market deficiencies that have resulted in the stagnant market, address the public health priorities that reflect the growing need for a sustainable solution to AMR, and operate within implementation constraints. Due to the complexity of the problem, we suggest first developing an incentive package that addresses the antibiotic market's failures. This package can then be enhanced to attend remaining public health objectives such as antibiotic conservation and patient access. The set of available incentives from which to create a comprehensive solution will be limited by government priorities, industry demands, and operational realities.

APPENDIX 1: RAPID REVIEW FLOW DIAGRAM



Adapted from the PRISMA Flow Diagram

APPENDIX 2: GENERALIZED SEARCH STRATEGY

Search Protocol:

Antibiotic OR antibiotics OR antimicrobial OR antibacterial OR anti-infective [title]

AND

Resistance OR resistant OR drug-resistance OR drug-resistant [title/abstract]

AND

Research OR development OR “R&D” OR innovation [title/abstract]

AND

Incentive OR incentives OR policy OR policies OR mechanism OR mechanisms OR “business model” OR “business models” OR strategy OR strategies [title/abstract]

APPENDIX 3: EXPERT INPUT

Experts that have assessed the identified set of strategies:

- Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, US Food and Drug Administration
- Mr. Bob Guidos, Senior Policy Coordinator, Center for Drug Evaluation and Research, US Food and Drug Administration
- Dr. Gregory Frank, Program Officer for Science & Research Policy, Infectious Disease Society of America
- Ms. Amanda Jezek, Vice President, Public Policy & Government Affairs, Infectious Disease Society of America
- Professor Kevin Outterson, Professor of Law, Boston University School of Law/ Faculty Affiliate, Center for Communicable Disease Dynamics, Harvard University
- Professor Aidan Hollis, Director, Incentives for Global Health/ Professor of Economics, University of Calgary
- Dr. Patrick Vink, Senior Vice President, Cubist Pharmaceuticals
- Mr. Chip Thresher, Government Affairs Graduate Fellow, Cubist Pharmaceuticals
- Dr. John Rex, Head of Infection & Global Medicines Development, AstraZeneca Pharmaceuticals[2]

[2] Contributed strategy not identified in literature search

APPENDIX 4: ADVANTAGES AND DISADVANTAGES OF INCENTIVES

Evaluation of Incentives: Advantages and Disadvantages		
Push Incentives		
Incentive	**Advantages**	**Disadvantages**
Supporting open access to research	• Lowers antibiotic research costs[47] • Allows early identification of feasible targets[48] • Facilitates collaboration among developers[48] • Creates a knowledge commons that minimizes research duplications and speeds dissemination of new information and technology[11]	• Relies on goodwill of researchers, industry, and universities[11] • Patent culture may prohibit open source contributions[48] • Few open sources tools that go beyond online data repositories • Does not address the core bottleneck of the R&D process
Grants for scientific personnel	• Lowers competition for skilled researchers[11] • Can complement other collaborative efforts such as open access to research	• Research interest does not guarantee tangible results[11] • Funded scientists not committed to antibiotic R&D[11] • Long lead time for investment[49]
Direct funding	• Lowers early R&D costs that prohibit participation of SMEs[11] • Allows direct targeting of R&D towards specific priorities[11] • Expert technical and managerial help useful to SMEs with less experience	• Risk of project failure placed on funder[11] • Prone to problems of transparency and principal-agent discrepancies[11] • Risk of changing political agenda[11] • Not well suited to support late stages of development[50]
Conditional grants	• Adds element of antibiotic stewardship to the incentive of direct funding[12] • See advantages of direct funding	• Challenge to ensure developers honour their conservation commitments • See disadvantages of direct funding
Funding translational research	• Promotes synergy across the value chain[11]	• Potential for conflicts of interest[51] • May impose perverse incentives to researchers [51] • Requires new IP laws to address subsequent innovation born from collaboration
Tax incentives	• Easy to implement and familiar to governments; lower administration costs[11] • Reduces problems of information asymmetry[52] • Market remains in charge of determining where investment is profitable; government dictates broad goals • Allows firms to innovate in ways that suit their particular strengths[52] • Lowers incentive for firms to direct R&D towards high profit, short sighted projects [53] • Can be tailored to specifically benefit SMEs over Big	• No mechanism to control cost incurred by government[19] • Government is not able to direct R&D into areas of high social return; less transparent than direct funding[7] • Risk borne by government that funded R&D projects will fail[11] • Incentive to employ creative accounting to maximize tax claim [30] • Firms that make low revenues, generally SMEs, do not benefit from tax incentives[22,54]

	Pharma[19] • Allow knowledgeable firms, not governments, to dictate the allocation of R&D investments[17]	
Refundable tax credits	• Promotes participation of SMEs[20] • See advantages of tax incentives	• See disadvantages of tax incentives
Product development partnerships (PDPs)	• Allows sponsor to set the target product profile and guide development[30] • Non-profit PDPs reduce need to maximize profit through sales[11] • Spread funder risk over a portfolio of projects[11] • PDPs pool expertise from all aspects of the development process[23] • Appeal to Big Pharma that value a project as too risky or because the potential market will be too small[11] • Appeal to SMEs that lack the capital to overcome early stage development barriers[55]	• Financial risk borne by sponsor that a funded project may fail[7] • Challenge to manage the interests of multiple stakeholders[7] • Prone to problems of transparency and principal-agent discrepancies[37] • Government may not be best suited to determine viability a project[37]
Pull Incentives		
Outcome-based Pull Incentives		
Incentive	**Advantages**	**Disadvantages**
Lump sum monetary prize	• Rewards only successful antibiotics[11] • Promotes clear communication between funder and developer; avoids principal agent problems[11] • Requires minimal additional infrastructure or regulation • Can be offered by non-governmental organizations as well as governments • Strong incentive for developers to carry drug R&D through Phase III clinical trials[11]	• Does not help SME overcome initial R&D barriers[25] • All risk borne by developers[25] • Difficult to set optimal scope of reward[11] • Sets a maximum value for the drug thus limiting the level of R&D into the drug • Prone to changing political agenda[25] • Challenge to determine how to reward follow-on innovators[56]
Milestone monetary prizes	• Allow funder to direct R&D[11] • Pull SMEs through the entire R&D process[11] • See advantages of lump sum monetary prizes	• Risk of funding projects that ultimately fails[11] • See disadvantages of lump sum monetary prizes
Pay-for-performance (P4P)	• Prescribers and developers have a direct incentive to minimize overuse[11] • Can be implemented within existing regulatory frameworks • Allows government to establish clear stewardship goals and rewards[11]	• Technically challenging to monitor antibiotic effectiveness, resistance, and appropriate use • Difficult to use as a direct incentive to stimulate research • Measures may provide perverse incentives to game the system [11]
Patent buyout	• Funder gains control over antibiotic price and volume; supports conservation & access goals[11]	• All development risk borne by developer[25] • Requires large financial outlay from funder[10]

	• Rewards only successful development[11] • Promotes clear communication regarding antibiotic characteristics; avoids principal agent problem[11] • Funder can license out IP[11]	• High cost to buyout makes political support challenging • Industry barriers to public ownership of IP[25,57] • Risk of funding suboptimal drug; little remaining funding to purchase drug improvements[25,58] • New agency may be needed to manage acquisition of IP[25,59] • Pricing buyout technically difficult[10,25]
Payer license	• Funder gains control over antibiotic price and volume; supports conservation & access goals[10] • Permits competitive pricing for license if multiple players[10] • Rewards only successful development[11] • Not committed to rolling over license if drug becomes suboptimal [10] • Maintain patent ownership with developer [57]	• Requires annual renegotiations of licenses; expensive transaction cost[10] • Minimal R&D incentive over other mechanisms[10] • Pricing license technically difficult • Risk of changing political agenda • All development risk borne by developer
Optional reward	• Gives developer greater flexibility with regards to revenue source • See advantages of patent buyout[12]	• If developer chooses to keep the patent then there remains significant incentive to over-market the antibiotic • See disadvantages of patent buyout[12]
Research tournament	• Competition may stimulate an increase in quality of submissions[60] • Tournaments with multiple rounds allow for selection of a few promising ideas[60] • Attracts developers that believe they have a competitive advantage or a promising molecule [11]	• Collusion degrades the quality of submissions[24] • Winner not incentivized to produce and distribute product[11] • Risk of funding failed projects • Tournaments are not well suited to promote new drug development in the expensive and risky late stages of R&D[11] • SMEs may not have the resources to compete against Big Pharma, limiting the effect of competition[11]
Advanced market commitment (AMC)	• Only rewards successful development[11] • Price guarantee lowers risk for developer [11] • Prices are set based on a county's ability to pay; improves patient access[61] • Does not require significant changes in regulatory statutes or laws; reward determined through the market [26]	• Challenging to set drug specifications beforehand[11] • Maintains artificially high prices in some countries; limits patient access[11] • Government commitment to purchase may led to acquiring inferior products [11,12] • No guarantee on volume means developer revenues are still highly dependent on sales volume[11]
Antibiotic Health Impact Fund (AHIF)	• Antibiotics offered at marginal cost; improve access[62] • Reward based on health impact encourages firms to provide access to the poor or in developing countries where impact would likely be greatest[62] • Profitability of projects tied to global public health impact; aligns firm incentive with global priorities[62] • Fewer patent litigations as generic distribution would	• Original HIF would be voluntary; undermines conservation incentives of the HIF[62] • Requires substantial upfront payments • Does not provide any push for developing new AB; particularly a problem for SME • International coordination complicated • New global agency needed to manage AHIF[62]

	increase developer profits[62] • Incentive for developer to limit unnecessary use; opportunity to coordinate with hospitals and patients[62] • Funder only pays for health impact; cost effective use of public resources[62] • Global solution to a global problem; based on an internationally coordinated action plan[62]	• Industry barriers to public ownership of IP[25,63] • Global surveillance and QALY assessment of health impact pose significant cost and technical challenge [25,63] • Significant uncertainty over health impact reduce R&D incentive[25] • Challenge to determine which drugs meet the criteria for inclusion
Antibiotic Innovation Funding Mechanism (AIFM)	• Decouples profits from sales volume; reinforces conservation efforts [41] • Decouples profits from prices; improves equity of access [41] • Encourage open sharing of relevant information, materials, and technology [41] • Global solution to a global problem; based on an internationally coordinated action plan[41] • Consumption fee helps self-sustain the fund and encourage appropriate use[41] • Payments throughout development chain encourage SME participation[41]	• Tax may hinder appropriate use at point of care[38] • Monetary prizes must be significant to incentivize R&D[11] • Milestone prizes place risk on funder[11] • High cost to buyout makes political support challenging[11] • Difficult to set optimal scope of reward [11] • International coordination and politics complicates the management of the fund • Industry barriers to public ownership of IP [57,59]
Strategic Antibiotic Reserve (SAR)	• Acts as insurance policy against growing AMR, pandemics, or bioterrorism [10,40] • See advantages for patent buyout and payer license	• Exceptionally high public cost to buy first-in-class drug[10] • Risk of cross-resistance undermining drug effectiveness without benefit from use[64] • See disadvantages for patent buyout and payer license
Lego-regulatory Pull Incentives		
Incentive	**Advantages**	**Disadvantages**
Accelerated assessment and approval	• Lowers cost of developing antibiotics[11] • Speeds up access to antibiotics[65]	• May compromise safety & efficacy of approval process[31] • Slows approval process for non-antibiotic drugs 5 • Does not benefit SMEs that have difficulty reaching the clinical trial assessment stages[11] • Increase public cost to expedite review and fund quickly released antibiotics
Market exclusivity extensions	• Developer can recoup R&D costs that may not have been covered by a patent's effective life • Monopoly prices can reduce inappropriate use of antibiotics[66] • An indefinite patent could place the responsibility of an antibiotic's long term sustainability with developer[67]	• High prices limit patient access and place significant financial burden on health system[67] • Reduces pressure to develop new drugs[11] • Developer incentive to maximize sales before end of patent[53] • Delay generic entry and competition[7]

Wild card extensions/ transferable intellectual property rights (TIPR)	• Flexible reward that can be tailored to the stage of innovation the government wishes to incentivize[68] • Only rewards completed projects[11] • Sale of TIPR allows SMEs to benefit[11]	• No mechanism to ensure efficacy of new antibiotic[69] • Transfers a rent to consumers of blockbuster drugs TIPRs are applied to[69] • Distorts market signals by attaching reward to unrelated drug[70]
Conservation-based market exclusivity	• Makes developers financially accountable for antibiotic resistance[66] • Aligns industry profit goals with public antibiotic stewardship goals • See advantages of market exclusivity extensions	• Requires expensive monitoring of antibiotic effectiveness • Maintains artificially high prices; limits patient access and places significant financial burden on health system[11] • Does not prevent resistance outside the implementing country[71] • Cross-resistance can reduce effectiveness through no fault of developer[64]
Liability limitations	• Incentivizes antibiotics for bioterrorism which are difficult to thoroughly test[11] • No upfront costs to the government[11] • Promote R&D of rare bacterial pathogens that may have little financial return to the developer without exposing themselves to potential lawsuits[11]	• Extension of liability protection beyond those needed for national defense may instigate a slippery legal slope • Insulation from liability may incentivize companies to be more reckless and push for broader indications for usage; may require closer government monitoring[72]
Anti-trust waivers	• Encourages developers to hold antibiotics in reserve until needed [11] • Allows developers to cooperate to limit resistance [11]	• Discourages competition and entry of generics; maintains high prices and lowers access[11] • Lack of threat of generic entry may stifle innovation[69] • Once a single drug in a class loses its patent, the ability of developers to control resistance through collusion fails[67]
Sui generis rights	• Makes developers financially accountable for antibiotic resistance[11] • Encourage developers to be more conservative with indications and volume[11]	• Maintains high prices; hinders patient access places significant financial burden on health system • Unclear how this would affect the patent system as a whole[11] • Lack of threat of generic entry may stifle innovation [69]
Value-based reimbursement	• Natural incentive for R&D into novel and high priority antibiotics[66] • Society pays for what it benefits from and values[40] • Higher prices can minimize inappropriate use of antibiotics [40,73] • Dis-incentivizes low value knock on R&D • Opportunity for re-evaluation of reimbursement rates to reflect changes in antibiotic effectiveness [40]	• Requires a substantial increase in reimbursement rates [40] • Requires expensive and slow health technology assessment of many drugs on the market [40] • Does not directly provide early stage capital infusion needed by SMEs to overcome R&D barriers[11] • Strong link between developer revenue and sales volume; incentive to over-market and promote antibiotics
The Generating Antibiotics Incentives Now (GAIN) Act	• Government provides guidance and resources to developers to clarify authorization requirements & lego-regulatory processes[11] • See advantages of market exclusivity extensions and	• Eligibility definition is slow, inflexible and does not specify standards for safety and efficacy[10,74] • Does not include any provisions for antibiotic conservation and appropriate use of new antibiotics[75]

	accelerated assessment and approval	• GAIN market exclusivity extensions run concurrently with patent protection, and may not provide benefit to drugs that have a substantial period of exclusivity through their patent extension[76] • See disadvantages of market exclusivity extensions and accelerated assessment and approval
Limited Population Antibacterial Drug (LPAD) approval	• Improves antibiotic access for patients[46] • Lowers development costs[77] • Regulatory body can monitor a LPAD's safety & efficacy[46] • Encourages firms to R&D drugs that combat rare pathogens and newly resistant strains of bacteria[77] • Narrow indication encourages LPAD antibiotics to be prescribed conservatively[78]	• Difficult for physicians to administer an LPAD in accordance with its labelled indication as diagnostic services remain slow[77] • High prices on LPADs can prohibit patient access[77]
Priority review vouchers (PRVs)	• Facilitates faster patient access to drugs expedited with PRVs [33] • Ability to sell to other firms allows SMEs to benefit from the program[11] • Possibility for PRV application to blockbuster drugs draws Big Pharma to antibiotics market	• Creates competition uncertainty in the entire pharmaceutical market[7,33] • Requirement for holders to inform the FDA 1 year in advance of filling for a new drug application greatly diminishes value of a PRV[7] • May compromise safety & efficacy of approval process[31] • Reduced incentive to bring the antibiotic to market after the PRV has been sold[79] • PRVs in the EU are complicated by the decentralized regulatory system[11]
New technology add-on payment (NTAP)	• Lowers revenue uncertainty by ensuring patient access[76] • NTAP rewards only successful, novel innovation[76] • Program has resulted in a decrease in Medicare spending [80]	• Program's eligibility definition lacks clarity[80] • NTAP payments may be too low and do not provide enough of a mark-up to sufficiently incentivize developers[80] • Increased hospital reimbursement removes hospital efficiency incentives to conserve use of an antibiotic[10]
Developing an Innovative Strategy for Antimicrobial Resistant Microbes (DISARM) Act	• Reduces the reimbursement risk for the developer[81] • Only successfully developed antibiotics are funded[81] • Reimbursement is attached to antibiotic stewardship[81] • Brings together key stakeholders to find a solution • See advantages of NTAP	• See disadvantages of NTAP
Hybrid Incentives		
Incentive	**Advantages**	**Disadvantages**
Special drug designation status	• Orphan drug designation already exists in the US and EU[11] • Historically effective at stimulating R&D of drugs with poor reimbursement prospects	• Funding only covers clinical phases; minimal funding for necessary preclinical research[82] • Current orphan drug legislation focuses on long-term/chronic

	• Push funding promotes participation from SMEs[7] • See advantages of accelerated assessment & approval, market exclusivity extensions, direct funding, and tax incentives	diseases; broad spectrum antibiotics not suitable for this designation • High prices limit patient access and place significant financial burden on health system[11] • Developer incentive to maximize sales[11] • See disadvantages of accelerated assessment & approval, market exclusivity extensions, direct funding, and tax incentives
Options market for antibiotics (OMA)	• Allows countries to pool resources together and with NGOs to incentivize R&D[45] • Funders can diversify their risk across developers and between drugs at different stages of development[45] • SMEs can receive the needed early funding to overcome initial R&D barriers[45] • Potential for secondary market that brings needed capital and liquidity to market[45] • Allow previously benched antibiotics to be reinstated based on improved profitability prospects[45] • Funder's purchase commitment controls some sales volume; promotes conservation efforts[45] • Options strike price can be set at the drug's marginal cost which delinks profit from sales volume[45]	• Does not completely delink developer profit from sales volume unless the strike price is set at marginal cost • Early investment places significant risk on the investor[45] • Prone to principal-agent problems as developers may try to game the system to secure more funding[45] • Does not directly encourage follow-on innovation unless multiple projects are funded in early stages[45] • Technically challenging to price the call options[45]
Office of Health Economics (OHE) model	• Shares risk between funder and developer[83] • Partially de-links sales volume from developer profit; promotes conservation efforts[83] • Flexible local pricing allows price to reflect variation in resistance across regions[83]	• Challenge to determine an appropriate size of annual fee to generate investment • Local pricing may be difficult to implement in a free trade zone or within a single country • Unclear how follow-on innovation will be incentivized • Difficult to incorporate conservation criteria linked to annual payments
Antibiotic Conservation Effectiveness (ACE) Programme	• Integrates well into existing quality reporting metrics[40] • See advantages of conservation-based market exclusivity, anti-trust waivers, and value-based reimbursement[40]	• Significant public cost from regulatory changes and monitoring • See disadvantages of conservation-based market exclusivity, anti-trust waivers, and value-based reimbursement
Project BioShield Act	• Creates a guaranteed market to fill federal stockpile needs and establish a credible purchasing agreement[84] • Milestone payments help SMEs with early development costs[11] • Allows access to antibiotics not yet approved by FDA in	• Political indecision over purchase commitments has increased uncertainty for developers[7,81] • Annual funding makes long term planning difficult[11] • Contracts have generally been too small to attract Big Pharma [7] • Not specifically targeted at antibiotics useful to the public

	times of emergency[84] • See advantages of accelerated assessment and review, milestone prizes, direct funding, and AMCs	• Poor liability protection limits the effectiveness of the incentive[7] • See disadvantages of accelerated assessment and review, milestone prizes, direct funding, and AMCs
Rewarding Antibiotic Development and Responsible Stewardship (RADARS) Program	• All key components of program already exist in the US (NTAP, BARDA/ Project BioShield) [36] • Only rewards successful development • Reduces reimbursement risk for developer [36] • Delinks revenue from volume & price (if guarantee large); reinforce conservation efforts and equity of access [10]	• Higher prices afforded by NTAP erode the conservation efforts of the guarantee[10] • NTAP removes stewardship incentive of lower priced diagnostic related groups[10] • Hospital-based and US centric; difficult to scale up • Long period of NTAP risks overpaying for sub-optimal drug in the future [10]
Antibiotics as Public Goods	• Decouples profits from sales volume; reinforces conservation efforts [10] • Involves developing countries in R&D of antibiotics[34] • Focuses on early stage development; lowers barriers of entry for SME [34] • Open source approach encourages collaboration among all stakeholders (particularly developing countries)[39] • Public ownership allows marginal cost pricing; improves equity of access [10,34] • Global solution to a global problem; based on an internationally coordinated action plan	• Early stage patent buy-out places high-risk on funder [85] • Scientific risk with emphasizing only natural products as a source of new antibiotics[86]5 • Requires large financial outlay from funder • Industry barriers to public ownership of IP • New global agency required to publicly manage acquisition of patents[34] • Pricing buyout technically difficult • International coordination and politics complicates the management of the fund
LPAD Plus	• Decouples profits from sales volume; reinforces conservation efforts[10] • See advantages of LPAD Approval	• Can increase uncertainty of developer revenue [10] • Pricing conservation incentive technically difficult [10] • See disadvantages of LPAD Approval
WHO Global Consortium	• Funder gains control over antibiotic price and volume; supports conservation & access goals [10] • Push incentives encourage crucial participation of SMEs [11,17] • Push funding through entire value chain [42] • Public funding of clinical trials increases transparency and sharing of important clinical data [42,44] • Purchase commitments give strict control over volume and generic distribution[42] • Global solution to a global problem; based on an internationally coordinated action plan[42]	• Pricing buyout technically difficult [11] • Almost all risk borne by public [43] • Challenge to generate significant international funding for such as consortium [43] • Industry barriers to public ownership of IP [57] • New entity may be needed to manage the entire supply chain [43] • Risk funding projects which fail [11] • Pushback from animal sector [43,87] • Prone to principal-agent problem[11]
GlaxoSmithKline (GSK) Delinkage	• Funder gains control over antibiotic price and volume; supports conservation & access goals[10]	• Strategy not fully formulated [10] • Requires annual renegotiations of licenses; expensive

Model	• License negotiated prior to critical late stage trials; reduces developer risk[57] • Funder not forced to roll over license if antibiotic becomes suboptimal [10] • Push incentives encourage crucial participation of SMEs [57]	transaction cost [10] • Pricing license technically difficult • Early funding places financial risk on funder [11] • Enables developer inefficiency [11] • Prone to principal-agent problem [11]
Mechanisms to Fund Incentives		
Mechanism	**Advantages**	**Disadvantages**
Fast-track option (FTO) for funding	• Flexible funding to finance multiple types of incentives[88] • Efficiency gains for both the developer and the public[88] • Allows developers that do not wish to participate in antibiotic development to contribute funds[88]	• Only a funding mechanism and does not directly incentivize R&D • Fast regulatory review may compromise safety[7,31] • May require new auction system and coordination across[88]
Antibiotic Innovation and Conservation (AIC) fee	• Induces conservation of antibiotics through higher prices [37] • Fee can be adjusted to reflect value and risk of use of antibiotic[37] • Helps to sustain R&D funding programs and stewardship programs[37]	• Only a funding mechanism and does not directly incentivize R&D • Tax may hinder appropriate use at point of care[38]

APPENDIX 5: ASSESSMENT OF INCENTIVES

Criteria-based Assessment of Incentives							
Push Incentives							
Incentive	**Improves NPV?**	**Enables participation of SMEs?**	**Encourages participation of Big Pharma?**	**Facilitates cooperation & synergy?**	**Promotes antibiotic stewardship?**	**Improves patient access?**	**Minimizes barriers to implementation?**
Supporting open access to research	✓	✓	X	✓	X	X	✓
Grants for scientific personnel	✓	✓	X	X	X	X	✓
Direct funding	✓	✓	X	X	X	X	✓
Conditional Grants	✓	✓	X	X	✓	X	X
Funding translational research	✓	✓	X	✓	X	X	✓
Tax incentives	✓	X	✓	X	X	X	✓
Refundable tax credits	✓	✓	✓	X	X	X	✓
PDPs	✓	✓	✓	✓	X	X	✓
Pull Incentives							
Outcome-based Pull Incentives							
Incentive	**Improves NPV?**	**Enables participation of SMEs?**	**Encourages participation of Big Pharma?**	**Facilitates cooperation & synergy?**	**Promotes antibiotic stewardship?**	**Improves patient access?**	**Minimizes barriers to implementation?**
End prize	✓	X	✓	X	X	X	✓
Milestone prize	✓	✓	✓	X	X	X	✓
P4P	✓	X	X	X	✓	X	X
Patent buyout	✓	✓	X	X	✓	✓	X
Payer license	✓	X	✓	X	✓	✓	X

Research tournament	✓	X	X	X	X	X	✓
AMC	✓	X	✓	X	✓	✓	✓
AHIF	✓	X	✓	✓	✓	✓	X
AIFM	✓	✓	✓	X	✓	✓	X
SAR	✓	X	X	X	✓	X	✓
Lego-regulatory Pull Incentives							
Incentive	**Improves NPV?**	**Enables participation of SMEs?**	**Encourages participation of Big Pharma?**	**Facilitates cooperation & synergy?**	**Promotes antibiotic stewardship?**	**Improves patient access?**	**Minimizes barriers to implementation?**
Accelerated assessment and approval	✓	X	✓	X	X	✓	✓
Market exclusivity extensions	✓	X	✓	X	X	X	✓
TIPR	✓	X	✓	X	X	X	✓
Conservation-based market exclusivity	✓	X	✓	X	✓	X	X
Liability protection	✓	X	✓	X	X	X	X
Anti-trust waivers	X	X	X	✓	✓	X	X
Sui generis rights	✓	X	✓	X	✓	X	X
Value-based reimbursement	✓	X	✓	X	X	X	✓
GAIN Act	✓	X	✓	X	X	X	✓
LPAD Approval	✓	✓	X	✓	X	✓	✓
PRV	✓	X	✓	X	X	X	✓
NTAP	✓	X	✓	X	X	X	✓
DISARM Act	✓	X	✓	X	✓	X	✓
Hybrid Push-Pull Incentives							

Incentive	Improves NPV?	Enables participation of SMEs?	Encourages participation of Big Pharma?	Facilitates cooperation & synergy?	Promotes antibiotic stewardship?	Improves patient access?	Minimizes barriers to implementation?
Special drug designation status	✓	✓	✓	✓	X	✓	✓
OMA	✓	✓	✓	X	✓	✓	X
OHE model	✓	X	✓	X	✓	✓	✓
ACE Programme	✓	X	✓	X	✓	X	X
Project BioShield	✓	✓	✓	X	✓	X	✓
RADARS Program	✓	X	✓	✓	✓	X	✓
Antibiotics as public goods	✓	✓	✓	✓	✓	✓	X
LPAD Plus	✓	✓	X	✓	✓	X	X
WHO Global Consortium	✓	✓	✓	✓	✓	✓	X
GSK Delinkage Model	✓	✓	✓	X	✓	✓	X
Mechanisms to Fund Incentives							
Incentive	**Improves NPV?**	**Enables participation of SMEs?**	**Encourages participation of Big Pharma?**	**Facilitates cooperation & synergy?**	**Promotes antibiotic stewardship?**	**Improves patient access?**	**Minimizes barriers to implementation?**
FTO Funding	X	X	✓	X	X	X	X
AIC Fee	X	X	✓	X	✓	X	X

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