

Matthew Renwick, David M. Brogan and [Elias Mossialos](#)
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REVIEW ARTICLE

A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics

Matthew J Renwick¹, David M Brogan^{1,2} and Elias Mossialos¹

Despite the growing threat of antimicrobial resistance, pharmaceutical and biotechnology firms are reluctant to develop novel antibiotics because of a host of market failures. This problem is complicated by public health goals that demand antibiotic conservation and equitable patient access. Thus, an innovative incentive strategy is needed to encourage sustainable investment in antibiotics. This systematic review consolidates, classifies and critically assesses a total of 47 proposed incentives. Given the large number of possible strategies, a decision framework is presented to assist with the selection of incentives. This framework focuses on addressing market failures that result in limited investment, public health priorities regarding antibiotic stewardship and patient access, and implementation constraints and operational realities. The flexible nature of this framework allows policy makers to tailor an antibiotic incentive package that suits a country's health system structure and needs.

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INTRODUCTION

Infectious microbial organisms are becoming increasingly resistant to the existing arsenal of antibiotic drugs. Antibiotics are indispensable in treating serious infections like tuberculosis, meningitis and pneumonia, preventing surgical site infections and managing immunocompromised individuals.^{1,2} It is estimated that antimicrobial resistance (AMR) is directly responsible for 23 000 deaths annually in the United States and more than 25 000 in the European Union.^{3,4} A conservative estimate of the economic cost of bacterial resistance is \$55 billion dollars annually in the United States alone.⁵ Despite the necessity for new antibiotics, the development pipeline is constrained, especially for those that tackle lethal multidrug-resistant Gram-negative bacteria.⁶ Pharmaceutical and biotechnology firms are averse to investing in new classes of antibiotics because the market is risky and relatively unprofitable. There are promising new methods of antibiotic discovery and some novel antibiotics in development that may not translate into marketable products if firms do not perceive profit potential.^{7,8}

The antibiotics market has a number of characteristics that makes it financially unattractive to developers. First, antibiotics are less profitable than other drug categories because 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 duration.^{9,10} Second, the regulatory requirements for market approval in the United States and European Union have been uncertain and prone

to change, creating additional development risk.¹¹ Third, many pharmaceutical companies have reallocated scientific talent and capacity to more profitable opportunities, thereby diminishing what antibiotic expertise and economies of scale they originally possessed.^{6,12} Therefore, firms need to be further incentivized to invest in the discovery and development processes necessary to create marketable novel antibacterial drugs.

Investment in antibiotics can be incentivized through two broad strategies known as push and pull mechanisms.^{12,13} Push mechanisms reduce a firm's cost of researching and developing new drugs by distributing the expenditures across multiple parties. Examples of push incentives include increasing access to research, providing research grants, offering tax incentives and establishing public–private partnerships for sharing research and development (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 Program and the Options Market for Antibiotics.^{14,15}

The European Observatory on Health Systems and Policies conducted the last major review and assessment of these push and pull incentives in 2010.¹² Since then, numerous initiatives, programs and

¹LSE Health, Department of Social Policy, London School of Economics and Political Science, London, UK and ²Missouri Orthopaedic Institute, University of Missouri, Columbia, MO, USA

Correspondence: Professor E Mossialos, LSE Health, Department of Social Policy, London School of Economics and Political Science, Houghton Street, London WC2A 2AE, UK. E-mail: e.a.mossialos@lse.ac.uk

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collaborations have been implemented with the goal of developing innovative business models for antibiotics. The World Health Organization (WHO) is developing its Global Action Plan under stewardship of the Scientific and Technical Advisory Group on Antimicrobial Resistance.¹⁶ The European Commission's Innovative Medicines Initiative (IMI) is Europe's largest public-private incentive program that supports the rapid development of safe and effective medicines for patients.¹⁷ The IMI has established the New Drugs for Bad Bugs (ND4BB) initiative that aims to remove the barriers associated with antibiotic drug discovery and development through collaboration.¹⁸ Notably, DRIVE-AB is a subsidiary program within the ND4BB initiative specifically focused on developing new economic models for antibiotic development.¹⁹ The European Commission and European Investment Bank are also launching a new risk sharing and direct loans program to finance development of new antibiotics (L Matthiessen, 2015, personal communication). In the United Kingdom, Prime Minister David Cameron commissioned the O'Neill Review on Antimicrobial Resistance and in the United States President Barack Obama released the National Action Plan for Combating Antibiotic-Resistant Bacteria.^{20,21} Think tanks such as Chatham House, Brookings Institute, Pew Charitable Trusts and Wellcome Trust are involved in the global effort through active working groups and conferences that bring together policy and business leaders from around the world.²²

The purpose of this article is to systematically review published incentive strategies to promote antibiotic research and critically assess the advantages and disadvantages of each. A framework is also proposed to assist policy makers in selecting appropriate incentives. This approach focuses on correcting the key market failures that perpetuate minimal investment in the field, while addressing antibiotic stewardship and patient access concerns, and accounting for implementation constraints.

RESEARCH METHODOLOGY

A systematic 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.²³ 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 gray literature, and then validated through expert opinion. Gray literature is literature not formally published such as conference proceedings, reports, legal documents and press releases.

Identification, screening and eligibility assessment of peer-reviewed and gray literature

The search protocol for peer-reviewed journals (Figure 1) was operationalized through MEDLINE via PubMed, Scopus, Econlit, Business Source Complete and CINAHL. Where possible, search results were filtered to include only literature that focused on humans, was published in the past 10 years, was in English and was 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. 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.

Gray 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 their references for articles not already identified. Gray literature was further identified through a Google search for articles, PowerPoint presentations, advocacy statements and conference listings. Websites of key advocacy groups, think tanks and policy committees were identified and further searched for sponsored literature.

Analysis

A total of 46 unique incentive strategies were identified from the literature search. The strategies encompassed single incentives and policies as well as multifaceted business models combining multiple incentives, policies and conservation mechanisms.

Expert opinion

This set of 46 strategies was presented to experts in the field including academics, advocates, industry professionals and policy makers. A total of 26 experts were initially approached, 9 experts provided feedback and 1 new strategy was added to the consolidated list. Therefore, a total of 47 strategies were reviewed.

Postreview critical analysis

Following compilation of all the incentive strategies, the incentives were then critically analyzed using criteria identified from the literature as important to creating an effective incentive package. This critical analysis forms the basis for a framework for selecting an optimal incentive package.

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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]
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Figure 1 Generalized search protocol.

IDENTIFICATION AND EVALUATION OF INCENTIVE STRATEGIES

Push strategies

Push mechanisms (Figure 2) seek to make drug development more attractive to firms by lowering their costs of generating a new drug. These incentives are useful because they reduce the barriers to entry that preclude participation by small- and medium-sized enterprises (SMEs).²⁴ These smaller firms develop a majority of new drugs, yet frequently lack the capital to translate early preclinical research into clinical development.^{11,24–27} Anti-infectives, including antibiotics, have higher success rates than other drug categories in the final phases of development.²⁸ Therefore, early push funding can help companies reach the R&D stages that are likely to produce marketable products. In addition, an early-stage R&D payment is more valuable than an equal pull incentive paid at a later date because of the time value of money. Spellberg *et al.*²⁹ found that an early subsidy could be as much as 95% smaller than an equally effective future reward. Finally, these policy subsidies may be linked to discrete R&D stages or drug characteristics to ensure alignment of developer goals with public priorities.¹³

There is a possibility that push incentives will fund projects that fail.¹³ In addition, developers have asymmetrically more information than funders regarding a particular project's development. Thus, there is an opportunity for developers to misrepresent their probability of success and project goals in order to attain financing.¹² Finally, research subsidies may damage operational efficiency by reducing financial pressure to economize or funder guidance may overly constrain the innovative capability of a developer.^{12,13} The advantages and disadvantages of each push strategy, along with all other strategies, can be seen in Table 1.

Pull strategies

Outcome-based pull strategies. Outcome-based pull incentives (Figure 3) raise project valuation by increasing future revenue through promised monetary rewards. In contrast to push mechanisms, outcome-based pull incentives only compensate successful development. Given that all R&D risk is borne by the developer, firms are motivated to maximize efficiency and adhere to efficacy requirements set by the funder.^{13,30}

However, financial risk and uncertainty are substantial deterrents for many potential market participants. This is particularly relevant to SMEs that may lack the resources to move from early-stage research to late-stage clinical trials. It is also difficult to determine an appropriate magnitude for the prize that must sufficiently motivate developers

while remaining cost effective. 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.¹² Finally, an effective outcome-based pull system relies on a government that is willing to stand by long-term guarantees.

Lego-regulatory pull strategies. Lego-regulatory pull incentives (Figure 4) are government policies that indirectly facilitate higher market returns for firms that launch a new antibiotic. 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 size.¹²

However, like outcome-based mechanisms, the financial risk of R&D is borne by the developer, thus excluding those firms that do not have substantial capital to market a promising antibiotic. Furthermore, many lego-regulatory mechanisms involve market exclusivity extensions that may dampen competition and innovation. When patents are extended, generic manufacturers are prevented from entering the market earlier and originators are less inclined to develop successive antibiotics that could cannibalize their exclusive market.¹²

Hybrid strategies

Each push, outcome-based pull and lego-regulatory pull mechanism has distinct advantages and disadvantages, but none provide a comprehensive solution to address the market failures outlined above. There is an increasing consensus that a single approach is not an adequate solution.^{12,31} Therefore, a combination of the above incentives or a hybrid strategy (Figure 5) that balances the varying attributes of the mechanisms may be needed.

Mechanisms to fund incentives

Some proposed strategies focus on how to fund the incentives discussed above (Figure 6). These mechanisms are not incentives themselves, but could be used to augment an incentive package and relieve some of the financial burden inherent to incentivizing R&D of antibiotics.

FRAMEWORK FOR SELECTION OF INCENTIVE STRATEGIES

Market criteria to create an attractive and supportive environment for investment

A plethora of potential incentive strategies exist, each with their own merits, drawbacks and level of complexity. Therefore, a framework would be useful to assist policy makers in selecting a comprehensive

- *Supporting open access to research* – providing and sharing scientific databases and molecule libraries^{12,13}
- *Grants for scientific personnel* – funding training and development of personnel specializing in R&D of antibiotics^{12,13}
- *Direct funding* – subsidies offered to organizations for the R&D of novel antibiotics^{12,13}
- *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 launched¹⁰
- *Funding translational research* – funding for facilitating cooperation and interaction throughout the entire supply chain including research, commercial development, and clinical application^{12,13}
- *Tax incentives* – tax credits, allowances, or deferrals that are tied to early R&D and reduce a developer's current tax liability^{12,13}
- *Refundable tax credits* – tax credits that can be redeemed for cash instead of reducing current tax liability³⁹
- *Product development partnerships (PDPs)* – collaborative agreements to share development risk and reward between a public or quasi-public organization and one or more private developers (e.g. IMI and the ND4BB Initiative)^{12,13,32,40}

Figure 2 Push strategies. IMI, Innovative Medicines Initiative; ND4BB, New Drugs for Bad Bugs; R&D, research and development.

Table 1 Evaluation of incentive strategies: advantages and disadvantages

Strategy	Advantages	Disadvantages
Push strategies		
Supporting open access to research	Lowers antibiotic research costs ⁶⁰ Allows early identification of feasible targets ⁶¹ Facilitates collaboration among developers ⁶¹ Creates a knowledge commons that minimizes research duplications and speeds dissemination of new information and technology ¹²	Relies on goodwill of researchers, industry and universities ¹² Patent culture may prohibit open source contributions ⁶¹ Few open source 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 ¹² Can complement other collaborative efforts such as open access to research	Research interest does not guarantee tangible results ¹² Funded scientists not committed to antibiotic R&D ¹² Long lead time for investment ⁶⁴
Direct funding	Lowers early R&D costs that prohibit participation of SMEs ¹² Allows direct targeting of R&D towards specific priorities ¹² Expert technical and managerial help useful to SMEs with less experience	Risk of project failure placed on funder ¹² Prone to problems of transparency and principal-agent discrepancies ¹² Risk of changing political agenda ¹² Not well suited to support late stages of development ⁶⁹
Conditional grants	Adds element of antibiotic stewardship to the incentive of direct funding ¹³ See advantages of direct funding	Challenge to ensure developers honour their conservation commitments
Funding translational research	Promotes synergy across the value chain ¹²	See disadvantages of direct funding Potential for conflicts of interest ⁷¹ May impose perverse incentives to researchers ⁷¹ Requires new IP laws to address subsequent innovation born from collaboration
Tax incentives	Easy to implement and familiar to governments; lower administration costs ¹² Reduces problems of information asymmetry ⁷³ 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 ⁷³ Lowers incentive for firms to direct R&D towards high profit, short sighted projects ¹² Can be tailored to specifically benefit SMEs over large cap firms ⁷⁴ Allow knowledgeable firms, not governments, to dictate the allocation of R&D investments ²⁷ Promotes participation of SMEs ³⁹ See advantages of tax incentives	No mechanism to control cost incurred by government ⁷⁴ Government is not able to direct R&D into areas of high social return; less transparent than direct funding ³² Risk borne by government that funded R&D projects will fail ¹² Incentive to employ creative accounting to maximize tax claim ⁷⁷ Firms that make low revenues, generally SMEs, do not benefit from tax incentives ^{78,79}
Refundable tax credits	See advantages of tax incentives	See disadvantages of tax incentives
Product development partnerships	Allows sponsor to set the target product profile and guide development ⁷⁷ Non-profit PDPs reduce need to maximize profit through sales ¹² Spread funder risk over a portfolio of projects ¹² PDPs pool expertise from all aspects of the development process ⁸¹ Appeal to large cap firms that value a project as too risky or because the potential market will be too small ¹² Appeal to SMEs that lack the capital to overcome early-stage development barriers ⁸²	Financial risk borne by sponsor that a funded project may fail ³² Challenge to manage the interests of multiple stakeholders ³² Prone to problems of transparency and principal-agent discrepancies ⁴⁰ Government may not be best suited to determine viability a project ⁴⁰
Pull strategies		
<i>Outcome-based pull strategies</i>		
Lump sum monetary prize	Rewards only successful antibiotics ¹² Promotes clear communication between funder and developer; avoids principal-agent problems ¹² Requires minimal additional infrastructure or regulation Can be offered by nongovernmental organizations as well as governments Strong incentive for developers to carry drug R&D through phase III clinical trials ¹² Allow funder to direct R&D ¹² Pull SMEs through the entire R&D process ¹² See advantages of lump sum monetary prizes	Does not help SME overcome initial R&D barriers ⁴¹ All risk borne by developers ⁴¹ Difficult to set optimal scope of reward ¹² Sets a maximum value for the drug thus limiting the level of R&D into the drug Prone to changing political agenda ⁴¹ Challenge to determine how to reward follow-on innovators ⁸³
Milestone monetary prizes	Prescribers and developers have a direct incentive to minimize overuse ¹² Can be implemented within existing regulatory frameworks Allows government to establish clear stewardship goals and rewards ¹²	Risk of funding projects that ultimately fails ¹² See disadvantages of lump sum monetary prizes
Pay-for-performance	Funder gains control over antibiotic price and volume; supports conservation and access goals ¹² Rewards only successful development ¹² Promotes clear communication regarding antibiotic characteristics; avoids principal-agent problem ¹² Funder can license out IP ¹²	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 ¹²
Patent buyout	Funder gains control over antibiotic price and volume; supports conservation and access goals ¹⁰ Permits competitive pricing for license if multiple players ¹⁰ Rewards only successful development ¹² Not committed to rolling over license if drug becomes suboptimal ¹⁰ Maintain patent ownership with developer ⁵⁸	All development risk borne by developer ⁴¹ Requires large financial outlay from funder ¹⁰ High cost to buyout makes political support challenging Industry barriers to public ownership of IP ^{41,58} Risk of funding suboptimal drug; little remaining funding to purchase drug improvements ^{41,84} New agency may be needed to manage acquisition of IP ^{41,63} Pricing buyout technically difficult ^{10,41} Requires annual renegotiations of licenses; expensive transaction cost ¹⁰
Payer license	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 ¹³ See advantages of patent buyout	If developer chooses to keep the patent then there remains significant incentive to over-market the antibiotic ¹³ See disadvantages of patent buyout

Table 1 (Continued)

Strategy	Advantages	Disadvantages
Research tournament	Competition may stimulate an increase in quality of submissions ⁸⁵ Tournaments with multiple rounds allow for selection of a few promising ideas ⁸⁵ Attracts developers that believe they have a competitive advantage or a promising molecule ¹²	Collusion degrades the quality of submissions ³⁰ Winner not incentivized to produce and distribute product ¹² 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 ¹² SMEs may not have the resources to compete with large cap firms, limiting the effect of competition ¹² Challenging to set drug specifications beforehand ¹² Maintains artificially high prices in some countries; limits patient access ¹² Government commitment to purchase may lead to acquiring inferior products ^{12,13} No guarantee on volume means developer revenues are still highly dependent on sales volume ¹²
Advanced market commitment	Only rewards successful development ¹² Price guarantee lowers risk for developer ¹² Prices are set based on a country's ability to pay; improves patient access ⁸⁶ Does not require significant changes in regulatory statutes or laws; reward determined through the market ⁴²	Original AHIF would be voluntary; undermines conservation incentives of the AHIF ⁴³ Requires substantial upfront payments Does not provide any push for developing new antibiotic; particularly a problem for SME International coordination complicated New global agency needed to manage AHIF ⁴³ Industry barriers to public ownership of IP ^{41,87} Global surveillance and assessment of health impact pose significant cost and technical challenge ^{41,87} Significant uncertainty over health impact reduce R&D incentive ⁴¹ Challenge to determine which drugs meet the criteria for inclusion
Antibiotic Health Impact Fund	Antibiotics offered at marginal cost; improve access ⁴³ Reward based on health impact encourages firms to provide access to the poor or in developing countries where impact would likely be greatest ⁴³ Profitability of projects tied to global public health impact; aligns firm incentive with global priorities ⁴³ Fewer patent litigations as generic distribution would increase developer profits ⁴³ Incentive for developer to limit unnecessary use; opportunity to coordinate with hospitals and patients ⁴³ Funder only pays for health impact; cost effective use of public resources ⁴³ Global solution to a global problem; based on an internationally coordinated action plan ⁴³	Tax may hinder appropriate use at point of care ⁶² Monetary prizes must be significant to incentivize R&D ¹² Milestone prizes place risk on funder ¹² High cost to buyout makes political support challenging ¹² Difficult to set optimal scope of reward ¹² International coordination and politics complicates the management of the fund Industry barriers to public ownership of IP ^{58,63}
Antibiotic Innovation Funding Mechanism	Decouples profits from sales volume; reinforces conservation efforts ⁴⁴ Decouples profits from prices; improves equity of access ⁴⁴ Encourage open sharing of relevant information, materials, and technology ⁴⁴ Global solution to a global problem; based on an internationally coordinated action plan ⁴⁴ Consumption fee helps self-sustain the fund and encourage appropriate use ⁴⁴ Payments throughout development chain encourage SME participation ⁴⁴	May compromise safety and efficacy of approval process ^{67,68} Slows approval process for non-antibiotic drugs ¹² Does not benefit SMEs that have difficulty reaching the clinical trial assessment stages ¹² Increase public cost to expedite review and fund quickly released antibiotics High prices limit patient access and place significant financial burden on the health system ⁷⁰ Reduces pressure to develop new drugs ¹² Developer incentive to maximize sales before end of patent ¹² Delay generic entry and competition ³²
Strategic Antibiotic Reserve	Acts as insurance policy against growing AMR, pandemics, or bioterrorism ^{10,14} 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 ⁶⁵ See disadvantages for patent buyout and payer license Developer still incentivized to maximize sales before end of patent Challenge to determine an appropriate size of annual fee Difficult to incorporate key performance indicators linked to annual payments
Service-availability premiums	Partially decouples profits from sales volume; promotes conservation efforts ³¹ Acts as insurance policy against growing AMR, pandemics or bioterrorism ³¹ Shift responsibility of long-term patient access to the antibiotic to the developer ³¹ Reimburses the developer for all the ancillary services required for delivery of antibiotics, particularly in emergencies ³¹ The premiums can be linked to mutually agreed key performance and conservation indicators ³¹	
<i>Lego-regulatory pull strategies</i> Accelerated assessment and approval	Lowers cost of developing antibiotics ¹² Speeds up access to antibiotics ⁶⁶	
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 ⁴⁶ An indefinite patent could place the responsibility of an antibiotic's long-term sustainability with developer ⁷⁰	No mechanism to ensure efficacy of new antibiotic ⁴⁷ Transfers a rent to consumers of blockbuster drugs TIPP are applied to ⁴⁷ Distorts market signals by attaching reward to unrelated drug ⁷⁵ Requires expensive monitoring of antibiotic effectiveness Maintains artificially high prices; limits patient access and places significant financial burden on the health system ¹² Does not prevent resistance outside the implementing country ⁷⁶ Cross-resistance can reduce effectiveness through no fault of developer ⁶⁵
Wild-card extensions/ transferable intellectual property rights	Flexible reward that can be tailored to the stage of innovation the government wishes to incentivize ⁷² Only rewards completed projects ¹² Sale of TIPP allows SMEs to benefit ¹²	
Conservation-based market exclusivity	Makes developers financially accountable for antibiotic resistance ⁴⁶ Aligns industry profit goals with public antibiotic stewardship goals See advantages of market exclusivity extensions	
Liability limitations	Incentivizes antibiotics for bioterrorism that are difficult to thoroughly test ¹² No upfront costs to the government ¹² Promote R&D of rare bacterial pathogens that may have little financial return to the developer without exposing themselves to potential lawsuits ¹²	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 ⁸⁰

Table 1 (Continued)

Strategy	Advantages	Disadvantages
Anti-trust waivers	Encourages developers to hold antibiotics in reserve until needed ¹² Allows developers to cooperate to limit resistance ¹²	Discourages competition and entry of generics; maintains high prices and lowers access ¹² Lack of threat of generic entry may stifle innovation ⁴⁷ Once a single drug in a class loses its patent, the ability of developers to control resistance through collusion fails ⁷⁰
Sui generis rights	Makes developers financially accountable for antibiotic resistance ¹² Encourage developers to be more conservative with indications and volume ¹²	Maintains high prices; hinders patient access and places significant financial burden on the health system Unclear how this would affect the patent system as a whole ¹² Lack of threat of generic entry may stifle innovation ⁴⁷
Value-based reimbursement	Natural incentive for R&D into novel and high priority antibiotics ⁴⁶ Society pays for what it benefits from and values ¹⁴ Higher prices can minimize inappropriate use of antibiotics ^{14,45} Dis-incentivizes low value knock-on R&D Opportunity for re-evaluation of reimbursement rates to reflect changes in antibiotic effectiveness ¹⁴	Requires a substantial increase in reimbursement rates ¹⁴ Requires expensive and slow health technology assessment of many drugs on the market ¹⁴ Does not directly provide early-stage capital infusion needed by SMEs to overcome R&D barriers ¹² Strong link between developer revenue and sales volume; incentive to overmarket and promote antibiotics
The Generating Antibiotics Incentives Now Act	Government provides guidance and resources to developers to clarify authorization requirements and regulatory processes ^{12,61} See advantages of market exclusivity extensions and accelerated assessment and approval	Eligibility definition is slow, inflexible and does not specify standards for safety and efficacy ^{10,88} Does not include any provisions for antibiotic conservation and appropriate use of new antibiotics ⁸⁹ 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 ⁵⁰ See disadvantages of market exclusivity extensions and accelerated assessment and approval
Limited Population Antibacterial Drug approval	Improves antibiotic access for patients ³⁸ Lowers development costs ⁹⁰ Regulatory body can monitor a LPAD's safety and efficacy ³⁸ Encourages firms to R&D drugs that combat rare pathogens and newly resistant strains of bacteria ⁹⁰ Narrow indication encourages LPAD antibiotics to be prescribed conservatively ⁹¹	Difficult for physicians to administer an LPAD in accordance with its labeled indication as diagnostic services remain slow ⁹⁰ High prices on LPADs can prohibit patient access ⁹⁰
Priority review vouchers	Facilitates faster patient access to drugs expedited with vouchers ⁹² Ability to sell to other firms allows SMEs to benefit from the program ¹² Possibility for voucher application to blockbuster drugs draws large cap firms to antibiotics market	Creates competition uncertainty in the entire pharmaceutical market ^{32,92} In the United States, requirement for holders to inform the Food and Drug Administration 1 year in advance of filing for a new drug application greatly diminishes value of a priority review voucher ³² May compromise safety and efficacy of approval process ^{67,68} Reduced incentive to bring the antibiotic to market after the voucher has been sold ⁴⁹ Vouchers in the European Union are complicated by the decentralized regulatory system ¹²
New technology add-on payment	Lowers revenue uncertainty by ensuring patient access ⁵⁰ NTAP rewards only successful, novel innovation ⁵⁰ Program has resulted in a decrease in Medicare spending ⁵¹	Program's eligibility definition lacks clarity ⁵¹ NTAP payments may be too low and do not provide enough of a mark-up to sufficiently incentivize developers ⁵¹ Increased hospital reimbursement removes hospital efficiency incentives to conserve use of an antibiotic ¹⁰ See disadvantages of NTAP
Developing an Innovative Strategy for Antimicrobial Resistant Microbes Act	Reduces the reimbursement risk for the developer ⁵³ Only successfully developed antibiotics are funded ⁵³ Reimbursement is attached to antibiotic stewardship ⁵³ Brings together key stakeholders to find a solution See advantages of NTAP	
21st Century Cures Act	Integrates an additional funding source that can be used for push incentives See advantages of LPAD approval and TIPR	Donation requirement may discourage firms from purchasing TIPR from successful antibiotic developers See disadvantages of LPAD approval and TIPR
Hybrid strategies		
Special drug designation status	Orphan drug designation already exists in the United States and European Union ¹² Historically effective at stimulating R&D of drugs with poor reimbursement prospects Push funding promotes participation from SMEs ³² See advantages of accelerated assessment and approval, market exclusivity extensions, direct funding, and tax incentives	Funding only covers clinical phases; minimal funding for necessary preclinical research ⁹³ Current orphan drug legislation focuses on long-term/chronic diseases; broad spectrum antibiotics not suitable for this designation High prices limit patient access and place significant financial burden on the health system ¹² Developer incentive to maximize sales ¹² See disadvantages of accelerated assessment and approval, market exclusivity extensions, direct funding and tax incentives
Options market for antibiotics	Allows countries to pool resources together and with nongovernmental organizations to incentivize R&D ¹⁵ Funders can diversify their risk across developers and between drugs at different stages of development ¹⁵ SMEs can receive the needed early funding to overcome initial R&D barriers ¹⁵ Potential for secondary market that brings needed capital and liquidity to market ¹⁵ Allow previously benched antibiotics to be reinstated based on improved profitability prospects ¹⁵ Funder's purchase commitment controls some sales volume; promotes conservation efforts ¹⁵ Options strike price can be set at the drug's marginal cost that delinks profit from sales volume ¹⁵	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 ¹⁵ Prone to principal-agent problems as developers may try to game the system to secure more funding ¹⁵ Does not directly encourage follow-on innovation unless multiple projects are funded in early stages ¹⁵ Technically challenging to price the call options ¹⁵

Table 1 (Continued)

Strategy	Advantages	Disadvantages
Office of Health Economics' model	Shares risk between funder and developer ⁵⁵ Partially delinks sales volume from developer profit; promotes conservation efforts ⁵⁵ Flexible local pricing allows price to reflect variation in resistance across regions ⁵⁵	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 Significant public cost from regulatory changes and monitoring See disadvantages of conservation-based market exclusivity, anti-trust waivers and value-based reimbursement
Antibiotic Conservation Effectiveness Program	Integrates well into existing quality reporting metrics ¹⁴ See advantages of conservation-based market exclusivity, anti-trust waivers and value-based reimbursement ¹⁴	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 ⁹⁴ Milestone payments help SMEs with early development costs ¹² Allows access to antibiotics not yet approved by Food and Drug Administration in times of emergency ⁹⁴ See advantages of accelerated assessment and review, milestone prizes, direct funding and AMCs	Political indecision over purchase commitments has increased uncertainty for developers ^{32,53} Annual funding makes long-term planning difficult ¹² Contracts have generally been too small to attract large cap firms ³² Not specifically targeted at antibiotics useful to the public Poor liability protection limits the effectiveness of the incentive ³² See disadvantages of accelerated assessment and review, milestone prizes, direct funding, and AMCs
Rewarding Antibiotic Development and Responsible Stewardship Program	All key components of program already exist in the United States (NTAP and Project BioShield) ⁵⁶ Only rewards successful development Reduces reimbursement risk for developer ⁵⁶ Delinks revenue from volume and price (if guarantee large); reinforces 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 United States centric; difficult to scale up Long period of NTAP risks overpaying for suboptimal 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 ⁵⁷ Focuses on early-stage development; lowers barriers of entry for SME ⁵⁷ Open source approach encourages collaboration among all stakeholders (particularly developing countries) ⁹⁵ Public ownership allows marginal cost pricing; improves equity of access ^{10,57} Global solution to a global problem; based on an internationally coordinated action plan	Early stage patent buy-out places high risk on funder ⁹⁷ Scientific risk with emphasizing only natural products as a source of new antibiotics ⁹⁶ Requires large financial outlay from funder Industry barriers to public ownership of IP New global agency required to publicly manage acquisition of patents ⁵⁷ 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 and access goals ^{10,13} Push incentives encourage crucial participation of SMEs ^{12,27} Push funding through entire value chain ³⁶ Public funding of clinical trials increases transparency and sharing of important clinical data ^{36,37} Purchase commitments give strict control over volume and generic distribution ³⁶ Global solution to a global problem; based on an internationally coordinated action plan ³⁶	Pricing buyout technically difficult ¹² Almost all risk borne by public ³⁵ Challenge to generate significant international funding for such as consortium ³⁵ Industry barriers to public ownership of IP ⁵⁸ New entity may be needed to manage the entire supply chain ³⁵ Risk funding projects which fail ¹² Pushback from animal sector ^{35,98} Prone to principal-agent problem ¹²
GlaxoSmithKline Delinkage Model	Funder gains control over antibiotic price and volume; supports conservation and access goals ¹⁰ License negotiated before critical late-stage trials; reduces developer risk ⁵⁸ Funder not forced to roll over license if antibiotic becomes suboptimal ¹⁰ Push incentives encourage crucial participation of SMEs ⁵⁸	Strategy not fully formulated ¹⁰ Requires annual renegotiations of licenses; expensive transaction cost ¹⁰ Pricing license technically difficult Early funding places financial risk on funder ¹² Enables developer inefficiency ¹² Prone to principal-agent problem ¹²
Mechanisms to fund incentives		
Fast-track option for funding	Flexible funding to finance multiple types of incentives ⁵⁹ Efficiency gains for both the developer and the public ⁵⁹ Allows developers that do not wish to participate in antibiotic development to contribute funds ⁵⁹	Only a funding mechanism and does not directly incentivize R&D Fast regulatory review may compromise safety ^{41,67,68} May require new auction system ⁵⁹
Antibiotic Corporate Bond	Flexible funding to finance multiple types of incentives ³¹ Allows developers that do not wish to participate in antibiotic development to contribute funds Patent extensions could be offered to nonpharmaceutical industries ³¹	Only a funding mechanism and does not directly incentivize R&D Offering patent extensions to nonpharmaceutical industries raises legal issues ³¹ Creates competition uncertainty in the markets patent extensions are offered Creates inequity in the patent system by allowing wealthy firms to outbid SMEs for patent extensions ³¹ High prices associated with market exclusivity limit patient access and place significant financial burden on the health system ³¹
Antibiotic Innovation and Conservation fee	Induces conservation of antibiotics through higher prices ⁴⁰ Fee can be adjusted to reflect value and risk of use of antibiotic ⁴⁰ Helps to sustain R&D funding programs and stewardship programs ⁴⁰	Only a funding mechanism and does not directly incentivize R&D Tax may hinder appropriate use at point of care ⁵²

Abbreviations: AHIF, Antibiotic Health Impact Fund; AMC, Advanced Market Commitment; AMR, antimicrobial resistance; GAIN Act, Generating Antibiotic Innovation Now Act; IP, intellectual property; LPAD, Limited Population Antibacterial Drug; NTAP, new technology add-on payment; PDP, product-development partnership; R&D, research and development; SME, small- and medium-sized enterprises; TIPR, transferable intellectual property rights; WHO, World Health Organization.

- *Lump sum monetary prize* – a large financial reward for the successful development of a novel antibiotic^{12,13,41}
- *Milestone monetary prizes* – incremental monetary rewards paid at various stages of the development process^{12,13,41}
- *Pay-for-performance (P4P)* – developers receive rewards for achieving quality goals relating to the antibiotic's consumption and resistance levels¹⁰
- *Patent buyout* – large end prize given in exchange for the intellectual property (IP) rights to a successfully developed antibiotic^{10,12}
- *Optional reward* – the developer can choose between a patent buyout reward or maintaining the patent for that antibiotic¹³
- *Payer license* – developer sells an annual license for unlimited access to an antibiotic at marginal cost¹⁰
- *Research tournament* – competitive milestone prizes awarded to the first developer(s) to reach certain checkpoints¹³
- *Advanced market commitment (AMC)* – an agreement to purchase a set volume of antibiotic for a pre-specified price upon successful development^{12,42}
- *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 drugs⁴³
- *Antibiotic Innovation Funding Mechanism (AIFM)* – a combination of monetary payments for licensing patents and a demand-side user fee to fund the prizes⁴⁴
- *Strategic Antibiotic Reserve* – 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^{14,45}
- *Service-availability premiums* – akin to an annual insurance premium, which is paid to a developer to ensure an antibiotic can be adequately produced and delivered when needed³¹

Figure 3 Outcome-based 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 specifications¹²
- *Market exclusivity extensions* – increase the period of IP and data exclusivity offered for an antibiotic^{12,46,47}
- *Wild card extensions/ transferable intellectual property rights (TIPR)* – extended IP protection that can be transferred to other drugs in a portfolio^{12,47}
- *Conservation-based market exclusivity* – market exclusivity of an antibiotic is tied to meeting effectiveness targets^{14,46}
- *Liability limitations* – legal protection against litigation in the event of injury or death related to antibiotics targeting bioterrorism and pandemic diseases¹²
- *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 antibiotics¹²
- *Sui generis rights* – offers market exclusivity to a firm for IP that has come off patent¹²
- *Value-based reimbursement* – Setting reimbursement prices for antibiotics based on health technology assessment of the drug's value to society^{12,46}
- *The Generating Antibiotics Incentives Now (GAIN) Act* – a US bill ratified in 2012, which provides five years of additional market exclusivity, priority review and fast track approval, and Food and Drug Administration guidance for antibiotic development⁴⁸
- *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 trials³⁸
- *Priority review vouchers* – 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^{12,13,32,49}
- *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^{50,51}
- *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 National Healthcare Safety Network^{52,53}
- *21st Century Cures Act* – a proposed US bill with provisions that offers qualified antibiotics a streamlined LPAD approval process and the option for up to twelve months of transferable market exclusivity; purchasers of this transferable market exclusivity are required to donate a portion of gross sales to AMR research and patient access programs⁵⁴

Figure 4 Lego-regulatory pull strategies. AMR, antimicrobial resistance; IP, intellectual property; US, United States.

and effective incentive package. Given the serious market failures outlined earlier, the key goal of any antibiotics incentive package is the creation of an attractive and supportive environment for investment. To achieve this, the following market criteria 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 Towse³² estimated the current

- *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^{12,13}
- *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 launch¹⁵
- *Office of Health Economics' model* – combines an AMC at a national or supranational level and local value-based pricing⁵⁵
- *Antibiotic Conservation Effectiveness (ACE) Program* – a comprehensive system involving value-based reimbursement, P4P payments, conservation-based market exclusivity, and anti-trust waivers¹⁴
- *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^{12,32}
- *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 market⁵⁶
- *Antibiotics as Public Goods* – milestone monetary prizes for early-stage antibiotic discovery, non-exclusive licensing for promising antibiotics, and an open source platform to share intellectual property, data, and clinical results⁵⁷
- *LPAD Plus* – the LPAD approval system combined with a monetary prize in return for conservation commitments and marginal cost pricing¹⁰
- *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 distribution³⁵
- *GlaxoSmithKline's Delinkage Model* – an annual payer license combined with a variety of pull incentives such as PDPs, tax credits, and research grants⁵⁸

Figure 5 Hybrid strategies. AMC, Advanced Market Commitment; EU, European Union; LPAD, Limited Population Antibacterial Drug; NTAP, new technology add-on payment; PDP, product-development partnership; P4P, pay-for-performance; US, United States.

- *Fast-track option for funding* – auction priority review vouchers to developers and use the earnings as push funding for antibiotic R&D⁵⁹
- *Antibiotic Corporate Bond* – government-guaranteed ten-year bonds financed through the sale of patent extension certificates³¹
- *Antibiotic Innovation and Conservation (AIC) fee* – a tax applied per prescription used to fund push incentives and stewardship programs⁴⁰

Figure 6 Mechanisms to fund incentives. R&D, research and development.

risk-adjusted NPV for developing an antibiotic to be –\$50 million. In contrast, the risk-adjusted NPV for a neurological drug is +\$720 million, and for a musculoskeletal drug this figure soars to +\$1.15 billion. 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 Towse³² suggest that a reasonable target for NPV should be \$200 million to make investment in antibiotics competitive with other therapeutic classes.

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. Munos²⁴ found that between the early 1980s to early 2000s, the proportion of all new drugs attributable to SMEs had increased from 23% to 70%. However, SMEs have much smaller capital reserves than large pharmaceutical companies, hindering the transition from initial research to expensive late-stage trials required for market approval. This is particularly detrimental to antibiotic development because the probability of clinical trial success for an antibiotic is positively weighted toward the later phases.³³ Thus, incentives that provide milestone payments, early seed money or reduce their cost of initial R&D allow smaller firms to move a promising antibiotic into the more favorable late-stage clinical trials.

Encourage participation by large pharmaceutical companies. Large market capitalization (large cap) pharmaceutical companies 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 often secure the needed funding. However, they are more concerned with the antibiotic market's uncertainty with regard to size, risk, volatility and regulation. Large cap companies need annual revenues of ~\$800 million for a drug to remain profitable.³⁴ In contrast, SMEs often only need to generate revenues of \$100 to \$200 million per year.³⁴ For this reason, large companies seek greater revenue certainty and regulatory transparency. These come from credible market commitments 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. The ideal incentive would reward collaboration by encouraging firms to cooperate to meet public health goals, share 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 to 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, lowering barriers for SME participation, encouraging large cap companies to invest in the market and facilitating cooperation and synergy among all stakeholders. The following framework (Table 2) is an incentive classification system based on these 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. As seen in Table 3, each incentive has been classified into one of the six types, depending on its ability to meet the market criteria.

Factoring in public health objectives: stewardship and access

Beyond creating a viable market for antibiotics, an incentive package should reinforce broader public health objectives pertaining to AMR. There are two key public health objectives that are interrelated with the economic aspects of an antibiotics market:

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

Promoting antibiotic stewardship. Research and development of antibiotics also needs to be sustainable in addition to being profitable. The traditional patent-based business model rewards developers through market exclusivity, providing the opportunity to command high prices. 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

overmarketing and overconsumption of antibiotics that has contributed to high levels of AMR. Simply increasing developer return on investment does not address this problem directly. Numerous experts have proposed antibiotic business models that reinforce conservation efforts by completely severing a developer's return on investment from sales volume and price (for example, Antibiotic Health Impact Fund (AHIF), Antibiotics as Public Goods and Rewarding Antibiotic Development and Responsible Stewardship Program (RADARS)). This concept is known as delinkage and is beneficial for three key reasons.¹⁰ First, it provides developers with a concrete return on investment that is extraneous to the market. Second, delinkage removes the motivation for developers to oversupply their antibiotic. Third, it facilitates access to new antibiotics for those who need them

Table 3 Classification of incentive strategies using the market-based framework

<i>Type 1: Broad-spectrum market incentives</i>	
PDP (Ps)	Antibiotics as public goods (H)
Special drug designation (H)	WHO global consortium (H)
<i>Type 2: Participation-focused incentives</i>	
Refundable tax credit (Ps)	OMA (H)
Milestone prizes (PI)	Project BioShield (H)
AIFM (PI)	GlaxoSmithKline's Delinkage (H)
<i>Type 3: Cooperation/synergy-focused incentives</i>	
Supporting open access (Ps)	Anti-trust waivers (LR)
Funding translational research (Ps)	RADARS Program (H)
AHIF (PI)	LPAD Plus (H)
LPAD (LR)	
<i>Type 4: SME-focused incentives</i>	
Grants for scientific personnel (Ps)	Patent buyout (PI)
Direct funding (Ps)	Optional reward (PI)
Conditional grants (Ps)	Strategic Antibiotic Reserve (PI)
Service-availability premiums (PI)	
<i>Type 5: Large cap-focused incentives</i>	
Tax incentives (Ps)	Sui generis rights (LR)
Lump sum monetary prize (PI)	Value-based reimbursement (LR)
Payer license (PI)	GAIN Act (LR)
AMC (PI)	Priority review vouchers (LR)
Accelerated assessment and approval (LR)	NTAP (LR)
Market exclusivity extensions (LR)	DISARM (LR)
Conservation-based market exclusivity (LR)	21st Century Cures Act (LR)
TIPR (LR)	Office of Health Economics' Model (H)
Liability protection (LR)	ACE Program (H)
<i>Type 6: Weak market incentives</i>	
P4P (PI)	Fast-track option for funding (F)
Research tournament (PI)	AIC fee (F)
Antibiotic corporate bond (F)	

Abbreviations: ACE, Antibiotic Conservation Effectiveness; AHIF, Antibiotic Health Impact Fund; AIC, Antibiotic Innovation and Conservation; AIFM, Antibiotic Innovation Funding Mechanism; AMC, Advanced Market Commitment; DISARM, Developing an Innovative Strategy for Antimicrobial Resistant Microbes; F, incentive funding mechanism; GAIN Act, Generating Antibiotic Innovation Now Act; H, hybrid push-pull incentive; LPAD, Limited Population Antibacterial Drug; LR, logo-regulatory incentive; NTAP, new technology add-on payment; OMA, options market for antibiotics; P4P, pay-for-performance; PDP, product-development partnership; PI, pull incentive; Ps, push incentive; RADARS, Rewarding Antibiotic Development and Responsible Stewardship; SME, small- and medium-sized enterprises; TIPR, transferable intellectual property rights; WHO, World Health Organization.

Table 2 Market-based framework for selection of incentive strategies

<i>Incentive type</i>	<i>Definition</i>
1 Broad-spectrum market incentives	Meet all four market criteria
2 Participation-focused incentives	Improve NPV and entice both SMEs and large cap firms to invest in antibiotic R&D but may not facilitate cooperation and synergy
3 Collaboration and 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 Large cap-focused incentives	Improve NPV and primarily benefit just large cap firms but may not facilitate cooperation and synergy
6 Weak market incentives	Incentives or funding mechanisms that only meet one of the four market criteria

Abbreviations: NPV, net present value; R&D, research and development; SME, small- and medium-sized enterprises.

most. Other experts advocate the use of demand-side antibiotic usage fees to internalize the negative externalities accompanying antibiotic use (for example, Antibiotic Innovation and Conservation (AIC) fee and Antibiotic Innovation Funding Mechanism (AIFM)). This fee can then be used to finance other incentive mechanisms such as milestone payments or end prizes.

Improving patient access to new antibiotics. Patient access to new antibiotics plays an important role in controlling the spread of AMR and preserving existing antibiotics. 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 universal access to pharmaceuticals. However, for those countries without complete public pharmaceutical coverage, 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. This may be overcome by transferring or licensing out a new antibiotic's patent to the government along with the responsibility of distribution and equitable access (for example, patent buyout and payer license). Other proposals streamline the regulatory approval process to allow new antibiotics with significant therapeutic value to reach the market faster (for example, Limited Population Antibacterial Drug (LPAD) approval and special drug status).

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, does not align developer promotion and marketing goals with conservation priorities. In this case, an additional incentive or incentives are necessary to augment this package. Aspects of conservation could be encouraged through conditional grants and pay-for-performance (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 overmarketing 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.

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 have been developed on a theoretical level, but rarely tested or deployed. Although design of appropriate incentives is challenging, it pales in comparison with the political, regulatory, industry and financial hurdles that may be faced during implementation. A comprehensive strategy that is unwieldy, too complex and financially unreasonable provides no advantage. 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 regulatory agency or governing body may be required to determine public health priorities, define the optimal number and depth of drug specifications linked to incentives, calculate socially fair rewards and monitor development progress. This is especially important as many of the recent proposals operate on a global scale and require coordination, input and agreement across borders (for example, AHIF, AIFM and WHO Global Consortium). This new organization could operate under a new agency or as part of an existing forum such as the G-20.

It is increasingly recognized that delinking sales volume from financial motivation to develop antibiotics is valuable to controlling AMR and facilitating equitable access to novel antibiotics.¹⁰ Several delinkage models such as patent buyouts, AHIF and AIFM are based on the concept of transferring intellectual property (IP) to the public domain that poses a major hurdle to implementation. From a public health perspective it makes sense to shift control of new antibiotic IP from the private to the 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. If transferring IP to the public domain is not feasible, these types of delinkage models become irrelevant. However, if this were the case, delinkage can still be created through incentives such as payer licenses, guaranteed revenue minimums or advanced market commitments (AMCs). Table 4 summarizes our assessment of each incentive strategy based on the market criteria, the public health objectives and implementation feasibility.

Example applications of the framework

Given the market failures endemic to antibiotic R&D, an incentive package should first correct market deficiencies. The framework outlined above is useful for this purpose. The package can then be augmented to address public health issues regarding antibiotic conservation and patient access. The following are three examples of the application of the above framework in devising an appropriate incentive strategy.

Scenario 1: A single type 1 incentive. The WHO's Global Consortium for stimulating antibiotic R&D is a well-rounded, hybrid model with 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 prizes for proven novel antibiotics, (4) public funding of clinical trials and (5) advance purchase commitments to preserve antibiotics.^{35,36} The WHO model attempts to create a product-development partnership (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 that can have an even greater impact overall because of 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.³⁷ Patent buyouts facilitate antibiotic stewardship by negating the need for excessive marketing or production. However,

Table 4 Criteria-based assessment of incentive strategies

Strategy	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation & synergy?	Promotes antibiotic stewardship?	Improves patient access?	Minimizes barriers to implementation?
Push strategies							
Supporting open access to research	✓	✓	✗	✓	✗	✗	✓
Grants for scientific personnel	✓	✓	✗	✗	✗	✗	✓
Direct funding	✓	✓	✗	✗	✗	✗	✓
Conditional Grants	✓	✓	✗	✗	✓	✗	✗
Funding translational research	✓	✓	✗	✓	✗	✗	✓
Tax incentives	✓	✗	✓	✗	✗	✗	✓
Refundable tax credits	✓	✓	✓	✗	✗	✗	✓
PDPs	✓	✓	✓	✓	✗	✗	✓
Pull strategies							
<i>Outcome-based pull strategies</i>							
Lump sum monetary prize	✓	✗	✓	✗	✗	✗	✓
Milestone prize	✓	✓	✓	✗	✗	✗	✓
P4P	✓	✗	✗	✗	✓	✗	✗
Patent buyout	✓	✓	✗	✗	✓	✓	✗
Payer license	✓	✗	✓	✗	✓	✓	✗
Research tournament	✓	✗	✗	✗	✗	✗	✓
Optional reward	✓	✓	✗	✗	✗	✗	✗
AMC	✓	✗	✓	✗	✓	✓	✓
AHIF	✓	✗	✓	✓	✓	✓	✗
AIFM	✓	✓	✓	✗	✓	✓	✗
Strategic Antibiotic Reserve	✓	✓	✗	✗	✓	✗	✓
Service -availability premium	✓	✓	✗	✗	✓	✓	✓
<i>Lego-regulatory pull strategies</i>							
Accelerated assessment and approval	✓	✗	✓	✗	✗	✓	✓
Market exclusivity extensions	✓	✗	✓	✗	✗	✗	✓
TIPR	✓	✗	✓	✗	✗	✗	✓
Conservation-based market exclusivity	✓	✗	✓	✗	✓	✗	✗
Liability protection	✓	✗	✓	✗	✗	✗	✗
Anti-trust waivers	✗	✗	✓	✓	✓	✗	✗
Sui generis rights	✓	✗	✓	✗	✓	✗	✓
Value-based reimbursement	✓	✗	✓	✗	✗	✗	✓
GAIN Act	✓	✗	✓	✗	✗	✗	✓
LPAD Approval	✓	✓	✗	✓	✗	✓	✓
Priority review vouchers	✓	✗	✓	✗	✗	✗	✓
NTAP	✓	✗	✓	✗	✗	✗	✓
DISARM Act	✓	✗	✓	✗	✓	✗	✓
21 st Century Cures Act	✓	✗	✓	✗	✗	✗	✓

Table 4 Continued

Strategy	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms ?	Facilitates cooperation & synergy?	Promotes antibiotic stewardship?	Improves patient access?	Minimizes barriers to implementation?
Hybrid strategies							
Special drug designation status	✓	✓	✓	✓	✗	✓	✓
OMA	✓	✓	✓	✗	✓	✓	✗
Office of Health Economics' model	✓	✗	✓	✗	✓	✓	✓
ACE Program	✓	✗	✓	✗	✓	✗	✗
Project BioShield	✓	✓	✓	✗	✓	✗	✓
RADARS Program	✓	✗	✓	✓	✓	✗	✓
Antibiotics as public goods	✓	✓	✓	✓	✓	✓	✗
LPAD Plus	✓	✓	✗	✓	✓	✓	✗
WHO Global Consortium	✓	✓	✓	✓	✓	✓	✗
GlaxoSmithKline Delinkage Model	✓	✓	✓	✗	✓	✓	✗
Mechanisms to fund incentives							
Fast-track option for funding	✗	✗	✓	✗	✗	✗	✗
Antibiotic Corporate Bond	✗	✗	✓	✗	✗	✗	✗
AIC Fee	✗	✗	✓	✗	✓	✗	✗

Abbreviations: ACE, Antibiotic Conservation Effectiveness; AHIF, Antibiotic Health Impact Fund; AIC, Antibiotic Innovation and Conservation; AIFM, Antibiotic Innovation Funding Mechanism; AMC, Advanced Market Commitment; DISARM, Developing an Innovative Strategy for Antimicrobial Resistant Microbes; GAIN Act, Generating Antibiotic Innovation Now Act; LPAD, Limited Population Antibacterial Drug; NPV, net present value; NTAP, new technology add-on payment; OMA, options market for antibiotics; P4P, pay-for-performance; PDP, product-development partnership; RADARS, Rewarding Antibiotic Development and Responsible Stewardship; SME, small- and medium-sized enterprises; TPIR, transferable intellectual property rights; WHO, World Health Organization.

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 incentives. The Options Market for Antibiotics (OMA) model is a hybrid mechanism that allows government or nongovernmental organization 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.¹⁵ 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 and 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.¹² Although 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 Effectiveness (ACE) Program is a hybrid strategy that combines outcomes-based and lego-regulatory pull mechanisms with the objective of promoting antibiotic conservation. The Program has four key components: (1) P4P payments centered 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.¹⁴ Given the pull-centric nature of the ACE Program, this incentive package particularly targets large cap pharmaceutical companies. 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 Program does not facilitate patient access nor promote cooperation and synergy between industry and the government. Thus, there is role for a 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.³⁸

In transitioning from single incentives to more complex, international business models, implementation becomes significantly more difficult. A feasible, yet comprehensive, incentive strategy likely will include a wide selection of smaller incentives that collectively address market and public health aspects as opposed to a revolutionary antibiotic business model. In our opinion, the 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.

CONCLUSION

Antimicrobial resistance is a complex health policy problem. Multiple market failures make it financially unattractive for pharmaceutical and biotechnology companies to invest in antibiotic discovery and development. This problem is complicated by incentives to oversell antibiotics and distribute based on ability to pay instead of need. This systematic literature review has identified 47 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 decision framework is needed to help 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. Because of the complexity of the problem, we suggest first developing an incentive package that addresses the core market failures. This can be further enhanced to achieve public health objectives such as antibiotic conservation and patient access. The above framework acknowledges that there are multiple viable solutions to stimulating antibiotic discovery and development that will ultimately be determined by government priorities, industry demands and operational realities unique to a particular country.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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